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REMARKS

Status of the Claims

Claims 1-12 and 14-34 are pending.

Claim 13 has been canceled.

Claims 18-20 were rejected under 35 U.S.C. §112, first paragraph.

Claims 1-12 and 14-34 were rejected under 35 U.S.C. §112, second paragraph.

Claims 1-4, 7, 8 and 18-34 are deemed allowable, but objected to as containing non-elected subject matter.

Restriction Requirement

The Examiner contends that the claims of the present application recite two separate classes of inventions, i.e., Group I (claims 1-12 and 14-34) is drawn to compounds having the formula of claim 1 where both rings A and B represent phenyl groups and one of R1 or R2 (variable Z) represents heteroaryl group, pharmaceutical compositions containing these compounds and a method of using these compounds (classified in class 548, subclass 195); and Group II (claims 1-34) is drawn to compounds other than defined for Group I, pharmaceutical compositions containing these compounds and a method of using these compounds (classified in classes 540, 544, 546, 549, 560, 564). Applicants hereby affirm the provisional election of Group I made with traverse on May 12, 2004, drawn to compounds, compositions and uses reading on claims 1-12 and 14-34.

The restriction requirement as set forth in the May 21, 2004, Office Action is traversed for the following reason. The compositions described by the Markush structure of original Claim 1 are substantially structurally similar and should not require multiple independent searches. For this reason, Applicants assert that examination of the entire application would not pose a serious burden. MPEP §803.01 addresses this situation as follows:

> [I]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, Applicants request withdrawal of the restriction requirement and reinstatement of the subject matter of Group II.

However, having elected the compositions of Group I, as required, Applicants have canceled claim 13 and amended the relevant portions of claims 1-12 and 14-34 to comply with the restriction requirement, as discussed hereinbelow. Accordingly claims 1-12 and 14-34 are pending.

Amendments

Specification

Certain portions of the instant specification were amended, as shown above, to correct typographical errors and to further clarify the disclosure. In particular, the paragraph and accompanying figure starting on line 17 of page 46 and ending on line 9 of page 47 were amended to clarify the definition of "heteroaryl." In doing so, a space was added after the comma in the phrase "or sulfur," and the phrase -- may be -- was inserted between the terms "such rings" and "fused," both changes being made on line 19 of page 46 of the instant specification, and six compounds were deleted from the figure on page 47 thereof.

On page 67, lines 20-22, of the specification, typographical errors were corrected by replacing the words "transrespressional" and "transscriptional" with -- transrepressional -- and -- transcriptional --, respectively.

Also on page 67 of the present specification, on line 23 thereof a typographical error was rectified by replacing the word "transrespressional" with -- transrepressional --, and on line 25 thereof a comma was added after the year "2002" for grammatical reasons and the attorney docket number in parenthesis was deleted from the disclosure.

Claims

Applicants amended the claims of the instant application for the reasons identified below. In claim 1, the word "from" was inserted in the limitation defining each group of variables R^e and R^f, R^g and R^h, R^i and R^j, and R^k and R^l to correct typographical mistakes. Also in claim 1, the limitation of variable Z was amended to comply with the above-referenced restriction requirement in that at least one of R^1 and R^2 represents a heteroaryl group. Additionally, both rings A and B were amended in claim 1 to represent phenyl groups in compliance with the restriction requirement. The amendments to variables R^1 and R^2 and rings A and B are further reflected in amendments made to the provisos of claim 1. The same amendments just described were also applied to instant method claims 24-27.

Claims 2-4 and 7-8 were further amended to comply with the restriction requirement.

Claim 8 was also amended to correct grammatical errors by adding commas before introducing structures C, D, E and F and by adding a period at the end of the claim.

Claim 13 was canceled, as previously discussed.

Claims 15 and 17 were amended to add a period at the end of each claim so that they are in proper grammatical form.

Claim 18 was amended for clarification reasons. In particular, the diseases of Claim dependent 19 were incorporated into Claim 18 as well as the term "NFκβ-induced transcription", a comma was added on the third line of the claim between the words "preventing" and "inhibiting." On line 6 of claim 18, the phrase "that is a" was replaced with the phrase -- wherein the -- and the word -- is -- was added between the words "disease" and "associated" to clarify the claim terminology. And, on line 7 of claim 18, the word "which" was replaced with the phrase -- the method -- to clarify the method claim language.

Claim 19 was canceled.

Claim 20 was amended to adjust dependency to Claim 18.

Claim 24 was amended, in addition to the aforementioned amendments, on line 17 of page 251 of the specification, by replacing the word "which" with the phrase -- the method -- to clarify the teaching of this claim. This same amendment was also made to claims 25-27.

Claim 25 was further amended, on line 1 of page 256 of the specification, by inserting the following definition for variable Z^1 after the atom "H" and before the comma: -- and Z^1 is CO_2H or CO_2 alkyl --. Also, the unnecessary variable R^x (and its definition) was replaced with "R". This amendment is discussed in more detail hereinbelow.

Claim 26 was amended to correct the teaching of redundant compounds by deleting the first instance of the compound and the teaching of the amine structure "$HNR^{1a}R^{2}$" from lines 1-8 on page 259 of the specification. Claim 26 was further amended, on line 12 on page 259 of the specification, to delete the limitation "and R^{1a} is R^1 other than H," to clarify the claim and to properly respond to the indefiniteness rejection under 35 U.S.C. § 112, second paragraph, as described herein below.

Applicants believe that the present amendments do not introduce new matter and do not broaden the scope of the claims. Further basis for the claim amendments appear below.

Section 112 Rejections

First paragraph, description/enablement

The Examiner has rejected Claims 18-20 for not enabling the claimed invention. Applicants hereby respond to each non-enabling rejection as follows.

Firstly, the Examiner avers that "[t]here is no teaching in the specification whether the instant compounds cause transrepression, transactivation, inhibit transrepression or inhibit transactivation" and that "[t]he utility of the instant compounds will be different based on agonist versus antagonist activity for transrepression or transactivation. There is no teaching either in the specification or prior art reference showing well known utility of prior art compounds which inhibit transrepression, cause transactivation or inhibit transactivation." In response, Applicants amend in-part and traverse in-part.

As discussed in the "Background of the Specification", compounds (e.g. glucocorticoids) demonstrating the transrepression of AP-1 and/or NFκβ-induced transcription have long been used to treat anti-inflammatory and immune-associated diseases and disorders. Accordingly, Claim 18 has been amended to specify the anti-inflammatory and immune-associated diseases and disorders of dependent Claim 19. Please see the numerous supporting references submitted in the December 8, 2003 IDS. Further as taught in the Specification, page 12, lines 5-6, the compounds of the instant invention have AP-1 inhibitory activity thereby demonstrating "transrepression" of AP-1 induced transcription. Moreover, as stated on page 32, lines 27-31 of the Specification, the compounds of the present invention also demonstrate transrepression of NFκβ-induced transcription and Claim 18 has been amended to reflect this. The description of the assays used to measure the foregoing activity are incorporated by reference to co-pending provisional application No. 60/396,907 (Specification, page 67). Thus, in view of what is known in the art, one of skill in the art would be able t use the teachings of the instant Specification to appreciate the activity of the instant compounds and practice the methods of claims 18 and 20.

Secondly, the Examiner states that:

> "[t]here are no working examples present in the specification showing efficacy of the instant compounds in vivo in known animal models of any disease state. The instant compounds of formula of claim1 encompasses hundreds of thousands of compounds based on the values of variables Ra to Ri, R and z and therefore, in absence of such teachings, guidance or presence of working examples, it would require undue experimentation to assess their agonist versus antagonist activity for transrepression or transactivation and hence their utility."

Applicants disagree with this rejection for the reasons stated above and assert that there are numerous examples given in the present application such that a person having ordinary skill in the art would be able to apply the disclosure and teachings therein, in conjunction with what is known in the art, to perform any *in vivo* disease state analysis.

For at least the reasons above, Applicants respectfully request withdrawal of the rejection of the claims for lack of enablement.

Second paragraph, indefiniteness

The Examiner has rejected claims 1-12 and 14-34 as being indefinite under the second paragraph of 35 U.S.C. §112 for several reasons.

Independent claims 1 and 24-27 were rejected for indefiniteness over the terms "stereoisomers," "prodrug ester," "heteroaryl" and "cycloheteroalkyl". In particular, the Examiner contends that "it is not clear which specific stereoisomer or prodrug ester is beging reffered here and furthermore, the steps for preparing them are not defined. Also, the terms – heteroaryl and cycloheteroalkyl – used for various variables are indefinite since the size of the ring, number and types of heteroatoms present in the ring are not defined."

In response, Applicants note that the term "prodrug ester" is clearly defined in the Specification, page 48, line 8 through page 49, line 5. Applicants also include with this amendment one of the many examples of literature detailing the nature of such prodrug esters (which includes several examples of well-known methods of preparation). *See e.g.* Wermuth et al, THE PRACTICE OF MEDICINAL CHEMISTRY, Chpt. 31, Designing Prodrug and Bioprecursors I: Carrier Prodrugs, pgs 767-680, Academic Press Lmtd (1996). Also, the term "stereoisomer" is well-defined in the Specification, page 49, line 27 through page 50, line 5. Moreover, one of skill in the art would be able to identify stereoisomers of compounds of Claims 1 and 24-27 based on well-known analyses of the three-dimensional structure of the molecule. *See e.g.* an excerpt from the textbook reference March, J., ADVANCED ORGANIC CHEMISTRY, 2ND ed. Chpt. 4 (Stereochemistry), pg 89-96 describing such an analysis. Finally, the terms heteroaryl" and "cycloheteroalkyl", including the ring size, number and types of heteroatoms present in the ring are specifically defined in the 'Definition of Terms' section on pages 46-47 of the present specification. Accordingly, given the teaching in the Specification combined with what is known in the art, a person having ordinary skill

in the art would understand the meaning of the terms "stereoisomers," "prodrug ester," "heteroaryl" and "cycloheteroalkyl" and Applicants respectfully request withdrawal of the indefiniteness rejection of claims 1 and 24-27.

Claim 18 was rejected due to the alleged indefiniteness of the terms "preventing," "inhibiting" and "GR-associated disease." In response, Applicant amend in-part and traverse in-part. Claim 18 has been amended to incorporate the GR-associated diseases listed in dependent claim 19 (now canceled) and believe this renders the indefiniteness rejection of claim 18 moot. With regard to the other terms, Applicants note that the terms "preventing" and "inhibiting" are self explanatory to a person skilled in the art. Additionally, the phrase "inhibiting onset of" is used in claim 18, as opposed to the term "inhibiting." The term "GR-associated disease" is specifically defined in the first full paragraph on page 30, lines 7-11, of the instant specification. Thus, Applicants respectfully request that the indefiniteness rejection of claim 18 be withdrawn.

Claim 25 was rejected because the variable Z^1 was not defined. Applicants appreciate the Examiner's careful review of the application and have amended Claim 25 to eliminate the unnecessary variable and definition of R^x and defined variable Z^1. Support for this amendment is found in Scheme B on pages 35-36 of the instant specification.

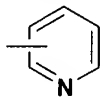
Claim 26 was also rejected for indefiniteness. Applicants have amended claim 26 to deletedthe duplicate portion of claim 26 and eliminate the unnecessary variable R^1. Support for this amendment is found in Scheme C on page 36 of the present specification.

For at least reasons discussed above, Applicants respectfully request withdrawal of the indefiniteness rejection of claims 1-12 and 14-34.

Allowable Subject Matter

The Examiner has kindly indicated that the instant compounds directed to elected Group I are allowable over the prior art. In particular, the compounds of the Pradines, et al. reference differ from the instant compounds "in having one of R^1 and R^2 variables as H and these compounds have been excluded by a proviso in the instant claim 1." This proviso (as presently amended to suit the restriction requirement) can be found on page 208, Section 1, subsection (1) of the application. The relevant portion of which is stated as follows:

"where Z is $CONR^1R^2$ and . . . (b) R^a and R^b are each hydrogen and one of R^c and R^d is alkyl, then

(1) at least one of R^1 and R^2 is heteroaryl, but where the heteroaryl is unsubstituted . . .  . . . then the other of R^1 and R^2 is other than hydrogen. . ."

Applicants appreciate the allowance of the compounds of elected Group I.

Objections

Claims 1-4, 7, 8 and 18-34 were objected to as containing non-elected subject matter. In view of the present amendments to the claims, Applicants believe this objection has been obviated.

FEES

No fees should be due. However, if it is determined that a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

SUMMARY

In view of the foregoing, it is requested that this case proceed to issuance. The Examiner is invited to contact the undersigned if it is believed prosecution could be expedited.

Respectfully submitted,

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Laurelee A. Duncan
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Reg. No. 44,093

Date: September 10, 2004

Four

Stereochemistry

In the previous chapters we have described what is known about electron distribution in organic molecules. In this chapter we shall discuss the three-dimensional structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. These three-dimensional structures are called *configurations*.

OPTICAL ACTIVITY AND CHIRALITY

A material which rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. Although the relationship between optical activity and chirality is empirical, it is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see p. 89). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This is both a necessary and a sufficient condition. This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true.

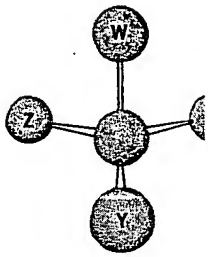
If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule (since superimposability is the same as identity), and in each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and the right-handedness of their orientations (Figure 1). Enantiomers have identical physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, though in equal amounts. The isomer which rotates the plane to the left (counterclockwise) is called the *levo isomer* and is designated (−), while the one which rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+).

2. They react at different rates with other chiral compounds. These rates may be so close together

[1] For excellent lengthy treatments of this subject, see Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962, "Elements of Stereochemistry," John Wiley & Sons, Inc., New York, 1969; Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, 1965; Wheland, "Advanced Organic Chemistry," 3d ed., pp. 195–514, John Wiley & Sons, Inc., New York, 1960; and Shriner, Adams, and Marvel, in Gilman, "Advanced Organic Chemistry," vol. 1, 2d ed., pp. 214–488, John Wiley & Sons, Inc., New York, 1943. Although the last review is not recent, most of it remains quite valid and useful.

[2] The IUPAC 1974 Recommendations, Section E, Fundamental Stereochemistry, give definitions for most of the terms used in this chapter, as well as rules for naming the various kinds of stereoisomers. They can be found in *Pure Appl. Chem.* 45, 13–30 (1976).



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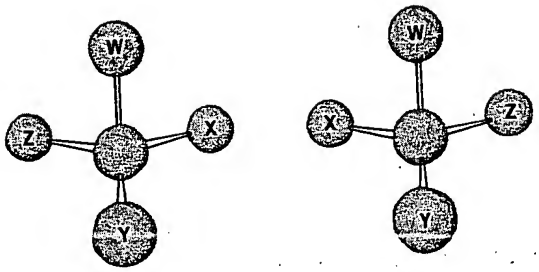

Figure 1 Enantiomers.

as to make the distinction practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. It is for this reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.

In general it may be said that enantiomers have identical properties in a symmetric environment, but in an asymmetric environment their properties may differ. Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if there is an optically active *catalyst* present; they may have different solubilities in an optically active *solvent;* they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, etc. In most cases these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive, since the rotations cancel. Such mixtures are called *racemic mixtures.*[3] Their properties are not always the same as those of the individual enantiomers. Usually the properties in the gaseous or liquid state, or in solution, are the same, since such a mixture is nearly ideal, but properties involving the solid state, such as melting points and solubilities, are often different. Thus racemic tartaric acid has a melting point of 204–206°C and a solubility in water at 20°C of 206 g/liter; while for the (+) or the (−) enantiomer, the corresponding figures are 170°C and 1390. The separation of a racemic mixture into its two optically active components is called *resolution.*

Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[4] and concentration (for solutions), the pressure (for gases), and the wavelength of light used. Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. Therefore, a number is defined, called the *specific rotation* $[\alpha]$, which is,

$$[\alpha] = \begin{cases} \dfrac{\alpha}{lc} & \text{for solutions} \\ \dfrac{\alpha}{ld} & \text{for pure compounds} \end{cases}$$

[3] Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book we shall use this expression to refer to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

[4] A good example is found in Kumata, Furukawa, and Fueno, *Bull. Chem. Soc. Jpn.* **43**, 3920 (1970).

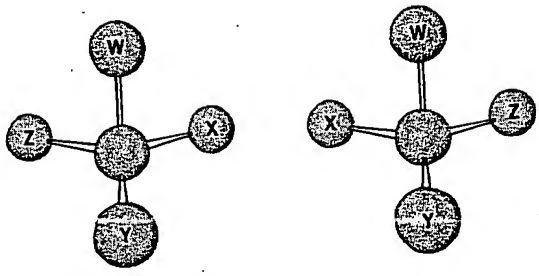

Figure 1 Enantiomers.

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[4] A good example is found in Kumata, Furukawa, and Fueno, *Bull. Chem. Soc. Jpn.* 43, 3920 (1970).

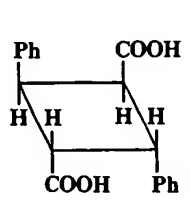
where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]^{25}_{546}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; i.e., $\lambda = 589$ nm. The molar rotation $[M]^t_\lambda$ is the specific rotation times the molecular weight, divided by 100.

It must be emphasized that although the value of α changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to $+4.36°$ at 20°C and $-1.86°$ at 90°C, though the molecular structure is unchanged. A consequence of cases like this is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior. Other cases are known in which the direction of rotation is reversed by changes in wavelength (this is common; see the discussion of optical rotatory dispersion on p. 135), solvent, and even concentration.[5] In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute-solvent interactions often cause nonlinear behavior. For example, $[\alpha]^{24}_D$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is $-5.0°$ at $c = 16.5$, $-0.7°$ at $c = 10.6$, $+1.7°$ at $c = 8.5$, and $+18.9°$ at $c = 2.2$.[6]

It should be noted that any single reading of the polarimeter must be ambiguous. A reading of say, 38°, could also be 218°, or 398°, or any number of the form $38 \pm 180n$ degrees, where n is any integer. However, it is relatively simple to determine the true reading by measuring another sample of the substance at a different concentration or cell length. For example, if the correct reading is 38°, a solution of one-fifth the concentration will give a value of 7.6°. If the correct reading was 218°, the new reading will be 43.6°, etc.

What Kinds of Molecules Display Optical Activity?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used, which are simpler to apply but not always accurate. One such test is the presence of a *plane of symmetry*. A plane of symmetry[7] (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry*, such as in α-truxillic acid (**1**), or an *alternating axis of symmetry* as in **2**.[8] A center of symmetry[7] is a point within an



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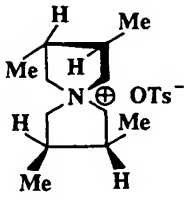

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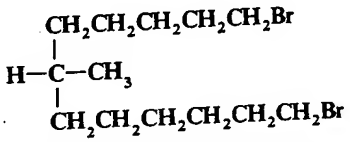
[5] For examples, see Shriner, Adams, and Marvel, Ref. 1, pp. 291–301.
[6] Krow and Hill, *Chem. Commun.* 430 (1968).
[7] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, "Elements of Stereochemistry," Ref. 1, pp. 6, 7.
[8] McCasland and Proskow, *J. Am. Chem. Soc.* 77, 4688 (1955).

object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[7] of order n is an axis such that when an object containing such an axis is rotated by $360°/n$ about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained which is indistinguishable from the original one.

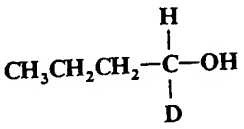
A molecule which contains just one *asymmetric carbon atom* (defined as a carbon atom connected to four different groups) is always chiral and hence optically active. As seen in Figure 1, such a molecule cannot have a plane of symmetry, whatever the identity of W, X, Y, and Z, so long as they are all different. However, the presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity may be present in molecules with no asymmetric atom and since some molecules with two or more asymmetric carbon atoms are superimposable on their mirror images and hence inactive. Examples of such compounds will be discussed subsequently.

Optically active compounds may be classified into several categories.

1. *Compounds with an asymmetric carbon atom.* If there is only one such atom, the molecule must be optically active. This is so no matter how slight the differences are among the four groups. For example, optical activity is present in



Optical activity has been detected even in such cases[9] as 1-butanol-1-*d*, where one group is hydrogen and another deuterium:[10]



However, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities,[11] and the optical activity of 5-ethyl-5-propylundecane was too low to be measurable at any wavelength between 2800 and 5800 Å.[12]

2. *Compounds with other quadrivalent asymmetric atoms.*[13] Any molecule containing an atom which has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si, Ge, N (in quaternary salts or N-oxides) and certain metals, such as Mn,[14] Cu, Be, and Zn, which form tetrahedral coordination compounds. In sulfones the sulfur bonds tetrahedrally, but since two of the groups are always oxygen, no optical activity can normally result. However, the preparation[15] of an optically active sulfone

[9] For reviews of compounds where chirality is due to the presence of deuterium or tritium, see Arigoni and Eliel, *Top. Stereochem.* 4, 127-243 (1969); and Verbit, *Prog. Phys. Org. Chem.* 7, 51-127 (1970).

[10] Streitwieser and Schaeffer, *J. Am. Chem. Soc.* 78, 5597 (1956).

[11] For a discussion of optical activity in paraffins, see Brewster, *Tetrahedron* 30, 1807 (1974).

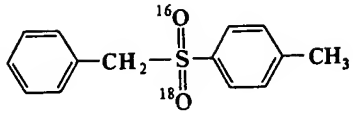
[12] Wynberg, Hekkert, Houbiers, and Bosch, *J. Am. Chem. Soc.* 87, 2635 (1965); Wynberg and Hulshof, *Tetrahedron* 30, 1775 (1974).

[13] For reviews of compounds with asymmetric atoms other than carbon, see Aylett, *Prog. Stereochem.* 4, 213-271 (1969); Belloli, *J. Chem. Educ.* 46, 640 (1969); and Sokolov and Reutov, *Russ. Chem. Rev.* 34, 1-12 (1965).

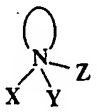
[14] Brunner, *Angew. Chem. Int. Ed. Engl.* 10, 249 (1971) [*Angew. Chem.* 83, 274].

[15] Stirling, *J. Chem. Soc.* 5741 (1963); Sabol and Andersen, *J. Am. Chem. Soc.* 91, 3603 (1969); Annunziata, Cinquini, and Colonna, *J. Chem. Soc., Perkin Trans. 1* 2057 (1972).

in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary:



3. Compounds with tervalent asymmetric atoms. Atoms with pyramidal bonding[16] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others.



For example, a secondary or tertiary amine where X, Y, and Z are different would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until recently all of them failed because of the *umbrella effect* (also called *pyramidal inversion*).[17] The umbrella effect is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer. For ammonia there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonias[18] (amines, amides, etc.). Two types of nitrogen atom invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an unshared pair. Even in such compounds, however, the umbrella effect has proved too rapid to permit isolation of separate isomers, and this goal was accomplished only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (3 and

trans

3

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4) were separated, and do not interconvert at room temperature.[19] Similarly, it has been shown that aziridines in which the ring nitrogen atom is connected to a nitrogen or oxygen atom are also conformationally stable. For example, nmr spectra show that two of the ring protons of 1-aminoaziridine (5) are not equivalent to the other two,[20] which indicates that the amino group

[16] For a review of the stereochemistry of the Group V elements, see Mann, *Prog. Stereochem.* 2, 196–227 (1958).

[17] For reviews of the mechanism of, and the effect of structure on, pyramidal inversion, see Lambert, *Top. Stereochem.* 6, 19–105 (1971); Rauk, Allen, and Mislow, *Angew. Chem. Int. Ed. Engl.* 9, 400–414 (1970) [*Angew. Chem.* 82, 453–468]; Lehn, *Fortschr. Chem. Forsch.* 15, 311–377 (1970); and Mislow, *Pure Appl. Chem.* 25, 549–562 (1968).

[18] For example, see Andose, Lehn, Mislow, and Wagner, *J. Am. Chem. Soc.* 92, 4050 (1970); Stackhouse, Baechler, and Mislow, *Tetrahedron Lett.* 3437, 3441 (1971).

[19] Brois, *J. Am. Chem. Soc.* 90, 506, 508 (1968). See also Lehn and Wagner, *Chem. Commun.* 148 (1968); Felix and Eschenmoser, *Angew. Chem. Int. Ed. Engl.* 7, 224 (1968) [*Angew. Chem.* 80, 197]; Kostyanovskii, Chervin, and Pan'shin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1354 (1968); Kostyanovskii, Samoilova, and Chervin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2705 (1968); *Tetrahedron Lett.* 719 (1969); Kostyanovskii, Markov, and Gella, *Tetrahedron Lett.* 1301 (1972). For a review, see Brois, *Trans. N.Y. Acad. Sci.* 31, 931-951 (1969).

[20] Brois, *Tetrahedron Lett.* 5997 (1968). See also Atkinson, *Chem. Commun.* 676 (1968); Brois, *J. Am. Chem. Soc.* 92, 1079 (1970); Ioffe and Koroleva, *Tetrahedron Lett.* 619 (1973).

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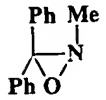

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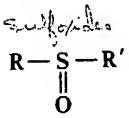

[21] Boyd, *Tetrahed*
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Trans. 2, 1575 (1973);
[22] Mannschreck,
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Tetrahedron Lett. 42
(1974).
[23] Müller and Es
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[24] Annunziata, F
[25] Prelog and Wi
[26] For reviews, se
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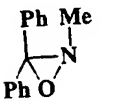
[27] Horner and F
[28] Reid, Stein, an

stays on the same side of the ring as two of the hydrogens and does not interconvert at room temperature. In none of the above cases, however, was a compound prepared which was optically active solely because of an asymmetric ternary nitrogen atom. This has now been accomplished with the syntheses of several oxaziridines, e.g., **6**.[21] Both enantiomers of **6**, a compound which is



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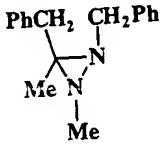

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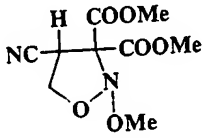

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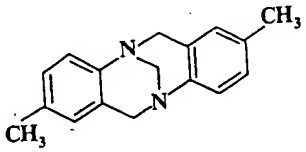
chiral solely because of an asymmetric ternary nitrogen atom, have been prepared. Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for diaziridines, e.g., **7**,[22] and for 1,2-oxazolidines, e.g., **8**,[23] even though in this case the ring is five-membered. However, note that the nitrogen atom here is connected to two oxygen atoms. The (+) isomer of **9** has been prepared.[24] It was completely racemized upon standing for 4 days at 0°C.

In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented, and such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **10** (Tröger's base) has been prepared.[25] Phosphorus inverts more slowly and arsenic still more slowly.[26] Optically active non-



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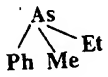

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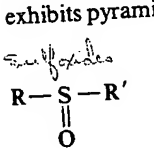
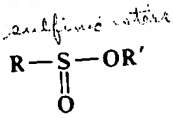
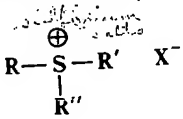
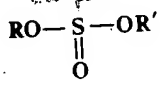
bridgehead phosphorus, arsenic, and antimony compounds have been resolved, e.g., **11**.[27] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites.[28] Examples of









[21] Boyd, *Tetrahedron Lett.* 4561 (1968); Boyd and Graham, *J. Chem. Soc. C* 2648 (1969); Boyd, Spratt, and Jerina, *J. Chem. Soc. C* 2650 (1969); Montanari, Moretti, and Torre, *Chem. Commun.* 1694 (1948), 1086 (1969). See also Mannschreck, Linss, and Seitz, *Justus Liebigs Ann. Chem.* 727, 224 (1969); Bjørgo and Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1575 (1973); Betżecki and Mostowicz, *J. Chem. Soc., Chem. Commun.* 244 (1975).

[22] Mannschreck, Radeglia, Gründemann, and Ohme, *Chem. Ber.* **100**, 1778 (1967); Mannschreck and Seitz, *Angew. Chem. Int. Ed. Engl.* **8**, 212 (1969) [*Angew. Chem.* **81**, 224]; Kostyanovskii, Zakharov, Zaripova, and Rudtchenko, *Tetrahedron Lett.* 4207 (1974); Kostyanovskii, Polyakov, and Markov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1601 (1974).

[23] Müller and Eschenmoser, *Helv. Chim. Acta* **52**, 1823 (1969); Dobler, Dunitz, and Hawley, *Helv. Chim. Acta* **52**, 1831 (1969).

[24] Annunziata, Fornasier, and Montanari, *J. Chem. Soc., Chem. Commun.* 1133 (1972).

[25] Prelog and Wieland, *Helv. Chim. Acta* **27**, 1127 (1944).

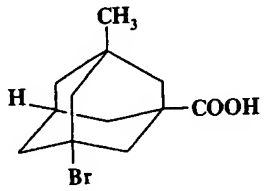
[26] For reviews, see Gallagher and Jenkins, *Top. Stereochem.* **3**, 1-96 (1968); Horner, *Pure Appl. Chem.* **9**, 225-244 (1964); and Kamai and Usacheva, *Russ. Chem. Rev.* **35**, 601-613 (1966). The last review also covers arsenic compounds.

[27] Horner and Fuchs, *Tetrahedron Lett.* 203 (1962).

[28] Reid, Stein, and Fahrney, *J. Am. Chem. Soc.* **89**, 7125 (1967).

each of these have been resolved.[29] An interesting example is (+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C but which has $[\alpha]_{280} = +0.71°$.[30]

4 *Suitably substituted adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active, and **12**, for example, has been resolved.[31]



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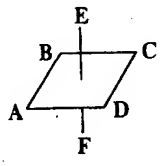
This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

5. *Compounds containing suitable substituted octahedral atoms.* Many metal ions, among them Cr(III), Pt(IV), and, most commonly, Co(III), form coordination compounds where six ligands surround the central atom. These ligands are usually found at the corners of an octahedron. If the ligands are sufficiently different, the compounds may be chiral. For example, if the six ligands are all different (as in **13**), the compound is theoretically resolvable, though no such example has yet been resolved.[32] However, many compounds with bidentate ligands, e.g., the *cis*-difluoro-bis(ethylenediamine)cobalt(III) ion (**14**), have been resolved.[33]



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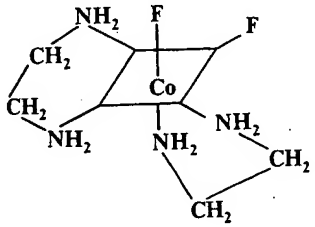

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6. *Restricted rotation giving rise to perpendicular disymmetric planes.* Certain compounds which do not contain asymmetric atoms are nevertheless chiral because they contain a structure which can be schematically represented as in Figure 2. For these compounds we can draw two perpendicular planes neither of which can be bisected by a plane of symmetry. If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

Biphenyls containing four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[34] In such compounds the two rings are in perpendicular

[29] For discussion, see Shriner, Adams, and Marvel, Ref. 1, pp. 419–423.
[30] Andersen, Colonna, and Stirling, *J. Chem. Soc., Chem. Commun.* 645 (1973).
[31] Hamill and McKervey, *Chem. Commun.* 864 (1969); Applequist, Rivers, and Applequist, *J. Am. Chem. Soc.* **91**, 5705 (1969).
[32] Wilkins and Williams, in Lewis and Wilkins, "Modern Coordination Chemistry," pp. 174–228, Interscience Publishers, Inc., New York, 1960. This is a review article on the stereochemistry of coordination compounds.
[33] Matoush and Basolo, *J. Chem. Soc.* **78**, 3972 (1956).
[34] When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, *Prog. Stereochem.* **4**, 1-42 (1969).

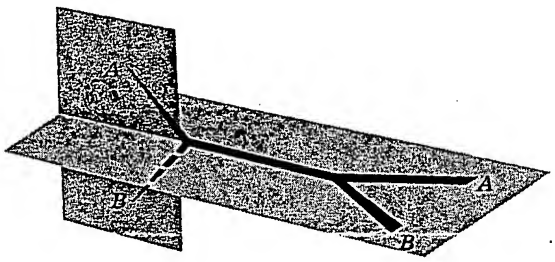
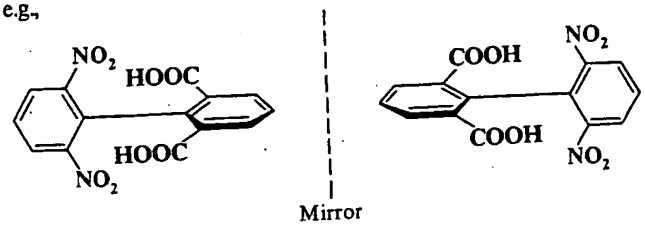


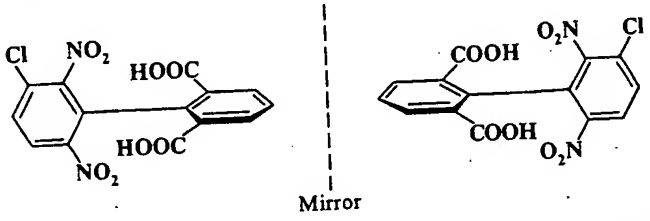
Figure 2 Perpendicular disymmetric planes.

planes. Three cases can be distinguished: both rings symmetric, one symmetric, neither symmetric. In the first case, e.g.,



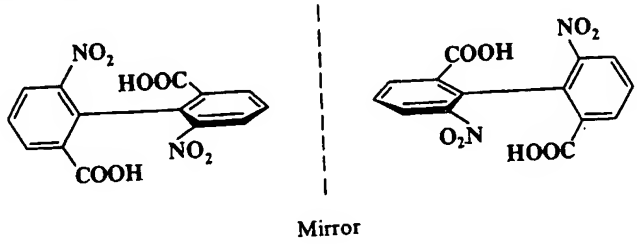
the molecule has two planes of symmetry. If a plane is drawn containing all atoms and groups in either ring, it is a *symmetrical* perpendicular bisector of the other ring. Such molecules are not chiral and, by the scheme in Figure 2, can be represented as $AA\cdots BB$.

In the second case only one ring is symmetric:



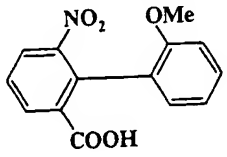
A plane drawn in the ring containing the nitro groups symmetrically bisects the other ring, but the plane of the ring containing the carboxyl groups is not a plane of symmetry. Nevertheless, one plane of symmetry is sufficient to make the compound achiral, and it is. The case can be symbolized as $AB\cdots CC$.

In the third case neither ring is symmetric:



There is no plane of symmetry, and the molecule is chiral; many such compounds have been resolved. This corresponds to $AB \cdots AB$. Of course $AB \cdots CD$ cases are also chiral. It is important to note that, if *either* ring is symmetrical, the molecule has a plane of symmetry and is achiral and that groups in the para position cannot cause lack of symmetry. Isomers which can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.

It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2'-bissulfonic acid.[35] In some cases, the groups may be large enough to slow rotation greatly but not prevent it completely. In such cases, optically active compounds can be prepared which slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.[36] Com-



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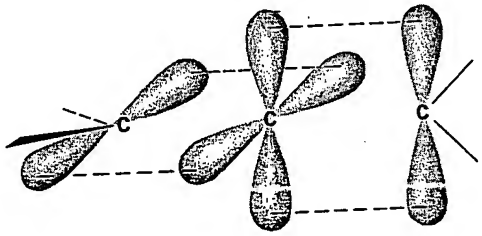
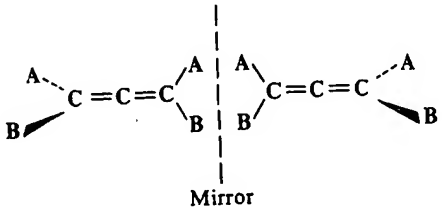
pounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.

Many analogous cases are known, where optical activity arises from hindered rotation of other types of aromatic ring, e.g., binaphthyls, bipyrryls, etc.

In allenes the central carbon is *sp*-bonded. The remaining two *p* orbitals are perpendicular to each other, and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two



remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Figure 2:



[35] Patterson and Adams, *J. Am. Chem. Soc.* 57, 762 (1935).
[36] Stoughton and Adams, *J. Am. Chem. Soc.* 54, 4426 (1932).

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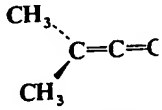

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[38] Nakagawa, Sh
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and Baes, *Tetrahedr*
(1973). Even pentah
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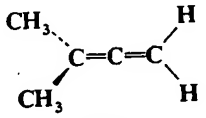
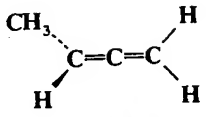
[40] For a review
727-738].

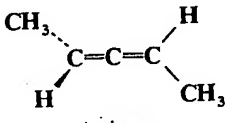
Like biphenyls, allenes are chiral only if both sides are dissymmetric.[37] Compounds corresponding to the three biphenyl cases are



Inactive
$AA \cdots BB$



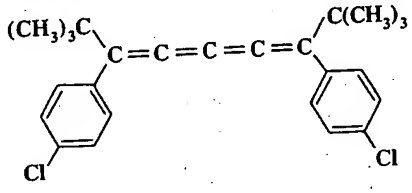
Inactive
$AB \cdots CC$



Active
$AB \cdots AB$

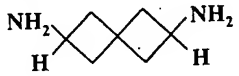
These cases are completely different from the cis-trans isomerism of compounds with one double bond (p. 113). In the latter cases the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.

When three, five, or any *odd* number of cumulative double bonds exist, orbital overlap causes the four groups to occupy one plane, and cis-trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes, and optical activity is possible. **16** has been resolved.[38]



16

Among other types of compounds which contain the system illustrated in Figure 2 and which are similarly chiral if they are $AB \cdots AB$ substituted are spiranes, e.g., **17**, and compounds with exocyclic double bonds, e.g., **18**.



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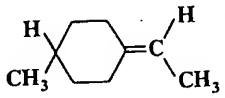


18

7. Chirality due to a helical shape. Several compounds have been prepared which are chiral because they have a shape which is actually helical and can therefore be left- or right-handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right-handedness. An example is hexahelicene[39] **(19)**, in which one side of the molecule must lie above the other because of crowding.[40] Another is *trans*-

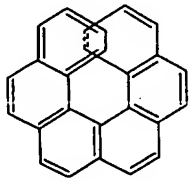
[37] For a review of chiral allenes, see Rossi and Diversi, *Synthesis* 25–36 (1973).

[38] Nakagawa, Shingū, and Naemura, *Tetrahedron Lett.* 802 (1961).

[39] Newman and Lednicer, *J. Am. Chem. Soc.* **78**, 4765 (1956). Optically active heptahelicene has also been prepared, as have higher helicenes: Flammang-Barbieux, Nasielski, and Martin, *Tetrahedron Lett.* 743 (1967); Martin, Flammang-Barbieux, Cosyn, and Gelbcke, *Tetrahedron Lett.* 3507 (1968); Martin, Morren, and Schurter, *Tetrahedron Lett.* 3683 (1969); Martin and Schurter, *Tetrahedron* **28**, 1749 (1972); Martin and Marchant, *Tetrahedron* **30**, 343 (1974); Martin and Baes, *Tetrahedron* **31**, 2135 (1975); Bernstein, Calvin, and Buchardt, *J. Am. Chem. Soc.* **94**, 494 (1972), **95**, 527 (1973). Even pentahelicene is crowded enough to be chiral: Goedicke and Stegemeyer, *Tetrahedron Lett.* 937 (1970); Bestmann and Roth, *Chem. Ber.* **107**, 2923 (1974).

[40] For a review of the helicenes, see Martin, *Angew. Chem. Int. Ed. Engl.* **13**, 649-660 (1974) [*Angew. Chem.* **86**, 727-738].

cyclooctene (**20**) (see p. 115), in which the carbon chain must lie above the plane of the double bond on one side and below it on the other.[41]



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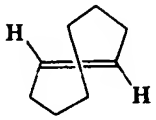

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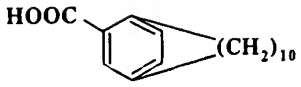
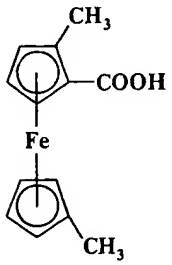


21

8. *Chirality caused by restricted rotation of other types.* Substituted paracyclophanes may be optically active, and **21**, for example, has been resolved.[42] In this case chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Metallocenes substituted with at least two different groups on one ring are also chiral.[43] More than



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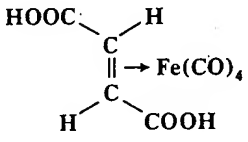

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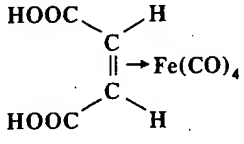
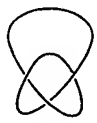


24

200 such compounds have been resolved, one example being **22**. Chirality is also found in other metallic complexes of suitable geometry.[44] For example, fumaric acid–iron tetracarbonyl (**23**) has been resolved.[45] The corresponding maleic acid compound (**24**) has a plane of symmetry and is not resolvable.

An interesting type of chirality has been proposed, though no example is yet known.[46] Rings containing 50 or more members should be able to exist as knots:



[41] Cope, Ganellin, Johnson, Van Auken, and Winkler, *J. Am. Chem. Soc.* **85**, 3276 (1963). Also see Cope, Banholzer, Keller, Pawson, Whang, and Winkler, *J. Am. Chem. Soc.* **87**, 3644 (1965); Cope, Hecht, Johnson, Keller, and Winkler, *J. Am. Chem. Soc.* **88**, 761 (1966); and Levin and Hoffmann, *J. Am. Chem. Soc.* **94**, 3446 (1972).

[42] Blomquist, Stahl, Meinwald, and Smith, *J. Org. Chem.* **26**, 1687 (1961).

[43] For reviews on the stereochemistry of metallocenes, see Schlögl, *Top. Stereochem.* **1**, 39–91 (1967), *Pure Appl. Chem.* **23**, 413–432 (1970).

[44] For reviews of such complexes, see Paiaro, *Organomet. Chem. Rev., Sect. A* **6**, 319–335 (1970).

[45] Paiaro, Palumbo, Musco, and Panunzi, *Tetrahedron Lett.* 1067 (1965); also see Paiaro and Panunzi, *J. Am. Chem. Soc.* **86**, 5148 (1964).

[46] Frisch and Wasserman, *J. Am. Chem. Soc.* **83**, 3789 (1961).

Such a knot would be nonsuperimposable on its mirror image. Catenanes and rotaxanes (see p. 85) can also be chiral if suitably substituted.[47]

Creation of a Chiral Center

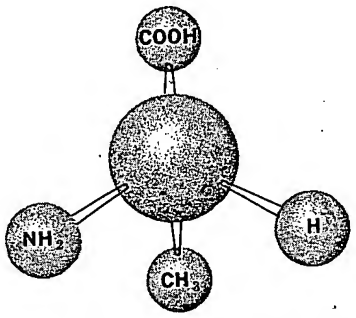
Any structural feature of a molecule which gives rise to optical activity may be called a chiral center. In many reactions a new chiral center is created, e.g.,

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

If the reagents and reaction conditions are all symmetric, the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[48] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

The Fischer Projection

For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Figure 1). However, when writing on paper or on the blackboard this is not feasible, and in 1891 Emil Fischer greatly served the interests of chemistry by inventing the Fischer projection, a method of representing tetrahedral carbons on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical:



$$\equiv \begin{array}{l} \text{COOH} \\ | \\ H_2N-C-H \\ | \\ CH_3 \end{array}$$

In order to obtain proper results from these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction they they may not be taken out of the plane of the blackboard or paper. Also they may not be rotated 90°, though 180° rotation is permissible:

$$\begin{array}{l} \text{COOH} \\ | \\ H_2N-C-H \\ | \\ CH_3 \end{array} = \begin{array}{l} CH_3 \\ | \\ H-C-NH_2 \\ | \\ \text{COOH} \end{array} \neq \begin{array}{l} NH_2 \\ | \\ CH_3-C-\text{COOH} \\ | \\ H \end{array}$$

[47] For a discussion of the stereochemistry of these compounds, see Schill, "Catenanes, Rotaxanes, and Knots," pp. 11–18, Academic Press, Inc., New York, 1971.

[48] There is one exception to this statement. In a very few cases racemic mixtures may crystallize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock and Wilson, *J. Chem. Educ.* 50, 455 (1973).

The Practice of Medicinal Chemistry

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Contents

31

Designing Prodrugs and Bioprecursors I: Carrier Prodrugs

CAMILLE G. WERMUTH, JEAN-CYR GAIGNAULT AND CHRISTIAN MARCHANDEAU

La façon de donner vaut mieux que ce que l'on donne.
The manner of giving counts more that what one gives
Piere Corneille, *Le Menteur*, Act 1, Scene 1.

THE PRACTICE OF MEDICINAL CHEMISTRY
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I. GENERAL INTRODUCTION

Therapeutic approaches based on molecular pharmacology mostly use *in vitro* models (membrane or enzyme preparations, cell or microorganism cultures, isolated organs, etc.). In the last decade they have led to the discovery of numerous potent and quite selective agents. As examples we can mention the GABAergic agonist muscimol,[1] the H_2 histamine antagonists burimamide and cimetidine,[2] the $GABA_A$ receptor antagonist gabazine,[3,4] the hydroxymethylglutaryl-CoA reductase inhibitor mevastatin,[5,6] the cholecystokinin antagonist asperlicin,[7] the anticancer drugs taxol[8,9] and neocarzinostatin[10] and the neurotensin antagonist SR 48692.[11]

However, the bioavailability of molecules exclusively screened through *in vitro* assays can be low. Because of the polarity of the functional groups present in the molecule, they may be poorly absorbed or incorrectly distributed. They may also, as a result of their vulnerability, be the subject of early metabolic destruction such as by first-pass effects or any other kind of degradation leading to a short biological half-life. For such molecules the *in vivo* administration is limited to the parenteral route and their clinical usefulness is thus restricted. Sometimes an adequate pharmaceutical formulation (microencapsulation, sustained-release or enterosoluble preparations) can overcome these drawbacks, but often the galenic formulation is inoperant and a chemical modification of the active molecule is necessary to correct its pharmacokinetic insufficiencies. This *chemical formulation* process, whose objective is to convert an interesting active molecule into a clinically acceptable drug, often involves design of a so-called 'prodrug'.

Initially the term prodrug was introduced by Albert to describe 'any compound that undergoes biotransformation prior to exhibiting its pharmacological effects'.[12] Such a broad definition includes accidental historical prodrugs (aspirin and salicylic acid), active metabolites (imipramine and desmethylimipramine) and compounds intentionally prepared to improve the pharmacokinetic profile of an active molecule. From this point of view the term 'drug latentiation' proposed by Harper[13] is more appropriate for prodrug design as it indicates that there is intention. Drug latentiation is defined as 'the chemical modification of a biologically active compound to form a new compound that, upon *in vivo* enzymatic attack, will liberate the parent compound'. Even this definition is too broad and a survey of the specialized literature led us to divide prodrugs into two classes: the carrier-prodrugs, and the bioprecursors.[14,15]

The *carrier-prodrugs* result from a temporary linkage of the active molecule with a transport moiety that is frequently of lipophilic nature. A simple hydrolytic reaction cleaves this transport moiety at the correct moment (e.g. bacampicillin, progabide). Such prodrugs are *per se* less active than the parent compounds, or even inactive. The transport moiety (carrier group) will be chosen for its nontoxicity and its ability to ensure the release of the active principle with efficient kinetics.

The *bioprecursors* do not involve a temporary linkage between the active principle and a carrier group but result from a molecular modification of the active principle itself. This modification generates a new compound, able to be a substrate for the metabolizing enzymes, the metabolite being the expected active principle. This approach exemplifies the active metabolite concept in the prospective application (e.g., sulindac, fenbufen).

II. THE CARRIER-PRODRUG PRINCIPLE

The carrier-prodrug principle (Fig. 31.1) consists of 'the attachment of a carrier group to the active drug to alter its physicochemical properties and then the subsequent enzyme attack to

release the active drug moie
nontoxic protective groups
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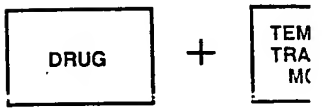

A well-designed carrier-p

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An example of prodru ampicillin derivatives.[20–22] a broad-spectrum antibiot about 40% of the drug is the same blood level one intramuscular injection. nonabsorbed part of the have been made to impro

Figure 31.2 represents both result from the ester labile ester. The main pro

(1) The absorption of
(2) The generation of
(3) The released carri for pivampicillin bacampicillin. Tl body. This ma pivampicillin.

release the active drug moiety'.[13] 'Prodrugs can thus be viewed as drugs containing specialized nontoxic protective groups used in a transient manner to alter or eliminate undesirable properties in the parent molecule'.[16]

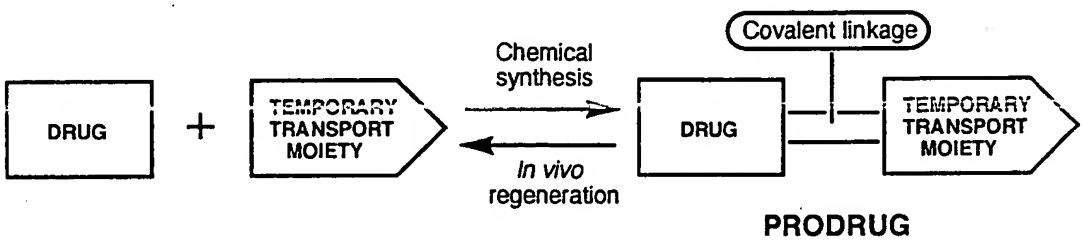


Fig. 31.1 The carrier-prodrug principle.[19]

A well-designed carrier-prodrug satisfies the following criteria.[17,18]

(1) The linkage between the drug substance and the transport moiety is usually a covalent bond.
(2) As a rule the prodrug is inactive or less active than the parent compound.
(3) The linkage between the parent compound and the transport moiety must be broken *in vivo*.
(4) The prodrug, as well as the transport moiety released *in vivo*, must be nontoxic.
(5) The generation of the active form must take place with rapid kinetics to ensure effective drug levels at the site of action and to minimize either direct prodrug metabolization or gradual drug inactivation.

An example of prodrug design taking into account these criteria is found in orally active ampicillin derivatives.[20–22] Ampicillin is one of the main β-lactam antibiotics. It is widely used as a broad-spectrum antibiotic but it suffers from poor absorption when administered orally: only about 40% of the drug is absorbed. In other words, to achieve the same clinical efficiency and the same blood level one must give two to three times more ampicillin by mouth than by intramuscular injection. The clinical tolerance of orally given ampicillin may be affected, the nonabsorbed part of the drug destroying the intestinal flora. Accordingly, numerous attempts have been made to improve these poor absorption properties.

Figure 31.2 represents two prodrugs of ampicillin: pivampicillin and bacampicillin. They both result from the esterification of the polar carboxylic group with a lipophilic, enzymatically labile ester. The main properties of these prodrugs can be summarized as follows.

(1) The absorption of these compounds is nearly quantitative (98–99%).
(2) The generation of free ampicillin in the bloodstream is rapid (less than 15 min).
(3) The released carrier molecules are formaldehyde and pivalic acid (trimethylacetic acid) for pivampicillin, and acetaldehyde, ethanol and carbon dioxide in the case of bacampicillin. These latter three compounds are natural metabolites in the human body. This may explain the better tolerance of bacampicillin compared to pivampicillin.

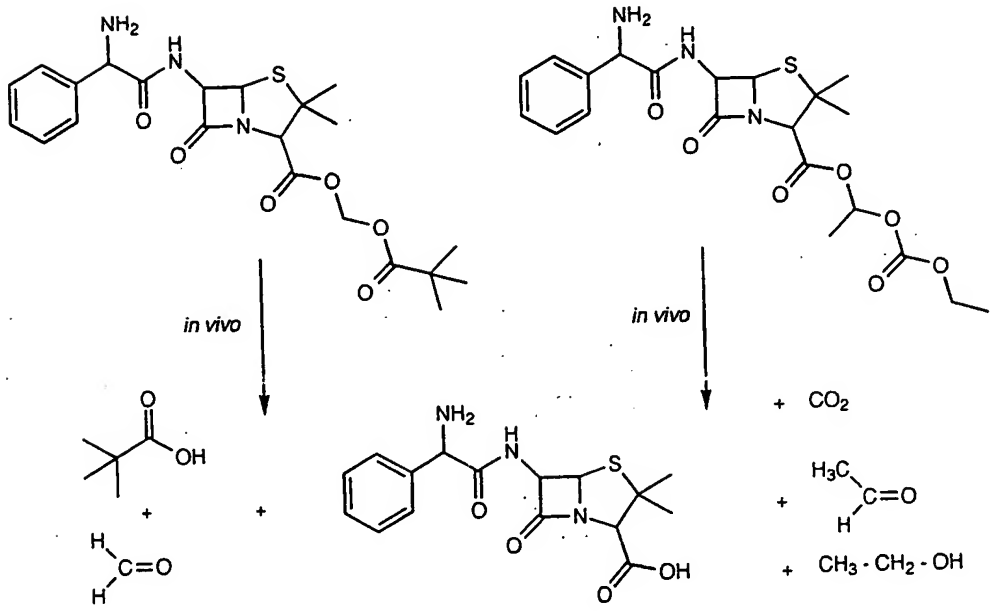
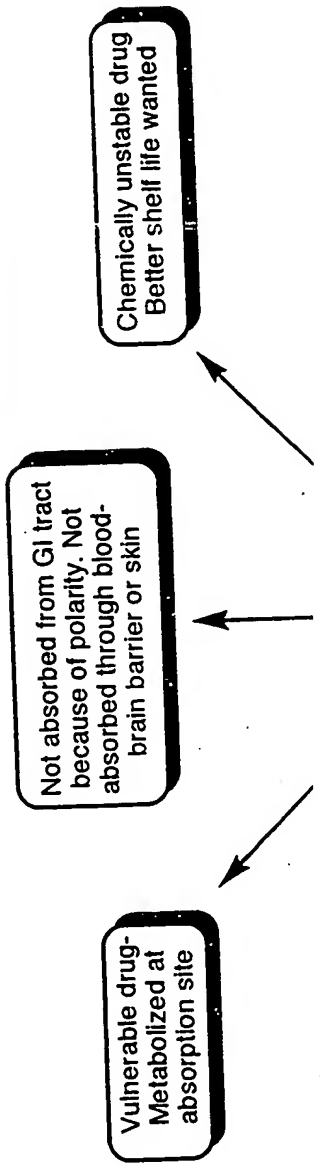


Fig. 31.2 Prodrugs derived from ampicillin.[20–22]

(4) The serum levels attained following oral administration of bacampicillin are similar to those obtained after intramuscular injection of an equimolecular amount of free ampicillin.
(5) Clinical trials confirm the efficiency and the safety of the prodrugs. Owing to their good absorption, the drugs are given at lower dosage than ampicillin: 0.8–1.0 g daily is sufficient in common infections as compared to 2.0 g daily for ampicillin.
(6) It has been shown, and this seems to be a rule for prodrugs, that pivampicillin and bacampicillin are inactive *per se*, the antibiotic potency appearing only *in vivo* after the release of free ampicillin.

III. PRACTICAL APPLICATIONS OF CARRIER-PRODRUG DESIGN

The domain of application of the prodrug approach is illustrated in Fig. 31.3. In practice, carrier prodrugs usually achieve one of the five following goals: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, improvement in drug formulation (stability, water solubility, suppression of an undesirable organoleptic or physicochemical property). The present chapter concentrates on problems related to the *pharmacokinetic phase*, such as improving the biomembrane passage, achieving site-specific delivery and obtaining sustained release. Prodrug problems related to the *pharmaceutical phase* (chemical solutions to formulation problems) will be treated in Chapters 34 and 35 (water solubility) and 38 (increasing chemical stability, dealing with mesomorphic crystalline forms, transforming liquids into solids, alleviating gastrointestinal irritation and painful injections, suppressing undesirable organoleptic properties, etc.). For applications in the field of insecticides, see Drabek and Neumann.[23]



andeau

+ CO_2

+ $CH_3 - CH_2 - OH$

bacampicillin are similar to molecular amount of free

drugs. Owing to their good npicillin: 0.8–1.0 g daily is r ampicillin.
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DRUG DESIGN

d in Fig. 31.3. In practice, eased lipophilicity, increased creased toxicity and adverse olubility, suppression of an ent chapter concentrates on ; the biomembrane passage, drug problems related to the will be treated in Chapters , dealing with mesomorphic astrointestinal irritation and etc.). For applications in the

Fig. 31.3 Shortcomings that may be overcome through chemical formulation.[17,19,24]

Bioactive compounds and drugs usually bear a limited number of polar functional groups suitable for prodrug synthesis. Among these, the most frequent are the alcoholic and the phenolic hydroxyls, the amino group, and the carboxylic function. The aim of the next sections is to illustrate how such groups can be used to prepare prodrugs with improved pharmacokinetic properties.

A. Improvement of the bioavailability and the biomembrane passage

The biomembrane passage of a drug depends primarily on its physicochemical properties and especially on its partition coefficient (Chapters 19 and 28). Thus, the transient attachment of a lipophilic carrier group to an active principle can provide better bioavailability, mostly by facilitating crossing of the cell membrane by passive diffusion. As well as peroral absorption, rectal absorption, ocular drug delivery and dermal drug delivery are also dependent on passive diffusion. Finally, lipophilic carriers can sometimes be useful in reducing first-pass metabolism.[25]

1. *Derivatization of drugs containing alcoholic or phenolic hydroxy groups*

Starting from hydroxylic derivatives, high lipophilicity can be obtained simply by esterification with lipophilic carboxylic acids. Dipivaloylepinephrine, for example (Fig. 31.4) crosses the cornea and is used in the treatment of glaucoma.[26] The β-blocker timolol contains a secondary amino group with a pK_a of 9.2 and, since this group is highly protonated at pH 7.4, the compound shows a low lipophilicity at physiological pH ($\log P = -0.04$), which in turn is unfavourable for corneal penetration. The corresponding butyryl ester has an increased lipophilicity ($\log P = 2.08$) and causes a 4- to 6-fold increase in the corneal absorption of timolol following topical administration to rabbits.[25]

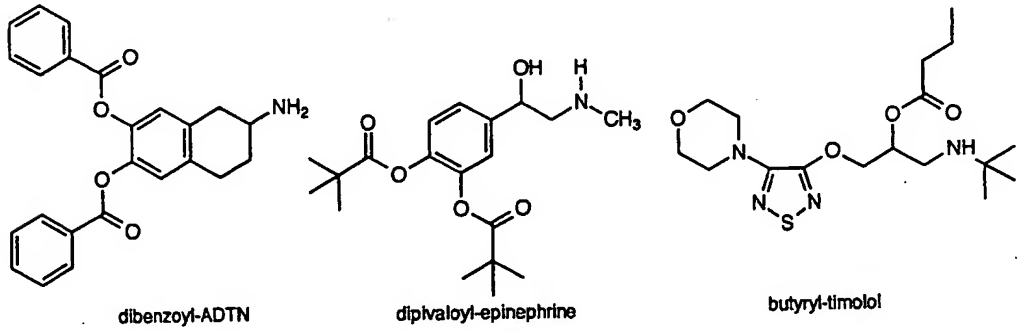

Fig. 31.4 Lipophilic prodrugs of hydroxy compounds with facilitated membrane penetration.[25–28]

In a similar manner, dibenzoyl-2-amino-6,7-dihydroxytetrahydronaphthalene (DB-ADTN) reaches the central nervous system, whereas the parent dopamine agonist ADTN does not.[27,28] For dipivaloylepinephrine and dibenzoyl-ADTN, the selective acylation of the phenolic hydroxyl groups was achieved in a strong acidic medium, the amino function being protected by protonation.[27,29] Acylated thymidine analogues such as 3′-*O*-hexyl-5′-amino-2′-

deoxythymidine are prodrug
(HSV-1).[30] Diacetyl and di
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dosing with the nonacylated
destroying the crystal lattice
arabinoside allowed a 5-fold
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2. *Derivatization of aldehydes and ke*

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3. *Derivatization*

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cetyl ester.[42]

Lipoidal prodrugs, i

deoxythymidine are prodrugs for topical application against herpes simplex type 1 viruses (HSV-1).[30] Diacetyl and dipropionyl guanine derivatives, given orally to mice, provided concentrations of the parent drug that were more than 15-fold higher than those observed after dosing with the nonacylated parent drug.[31] In augmenting the lipophilicity and simultaneously destroying the crystal lattice energy, the 2′,3′-diacetate of the antiviral agent 6-methoxypurine arabinoside allowed a 5-fold increase in bioavailability and a 3-fold increase in water solubility in comparison to the nonacetylated drug.[32] As a consequence, an intravenous formulation could be developed.

2. Derivatization of drugs containing a carbonyl function: aldehydes and ketones

The ethylene ketal derivative of prostaglandin E_2 (dinoprostone) possesses much improved solid-state stability (see Chapter 38). Functionalized spirothiazolidines of hydrocortisone and hydrocortisone 21-acetate (Fig. 31.5), prepared with cysteine esters or related β-aminothiols, have improved topical anti-inflammatory activity. It is speculated that the Schiff base intermediate formed upon ring-opening may accumulate in the skin by binding (through its SH function) to thiol groups in the skin.[33]

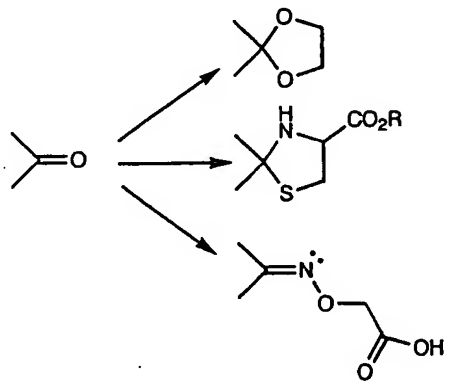

Fig. 31.5 Prodrug possibilities starting from aldehydes or ketones.

Simple and substituted oximes are biostable unless intramolecular assistance is provided. This is the case for the oximes derived from oxyamino acetic acid, which are possible water-soluble prodrugs of ketones and aldehydes (see Chapter 35).

3. Derivatization of drugs containing a carboxylic acid function

Lipophilic prodrugs can also be derived from a carboxylic function, the most commonly used derivatives being carboxylic esters. Simple esters of aliphatic alcohols are attractive as they are cheap to prepare, chemically stable, and yield harmless hydrolysis products.[34] Typical representatives of such prodrugs are tyrosine methyl ester,[35] nipecotic acid ethyl ester,[36] enalaprilat ethyl ester,[37,38] trandolapril,[39] γ-aminobutyric acid cetyl ester,[40,41] and methotrexate cetyl ester.[42]

Lipoidal prodrugs, in which the carboxyl function esterifies the free alcoholic hydroxyl of

1,2- or 1,3-diglycerides, are well absorbed and show high lymphotropism. Applied to the anti-inflammatory agent naproxen, this approach yielded the 2-ester of 1,3-dipalmitoylglycerol (Fig. 36.6), which produces less gastric irritation and higher plasma levels than the parent compound.[43]

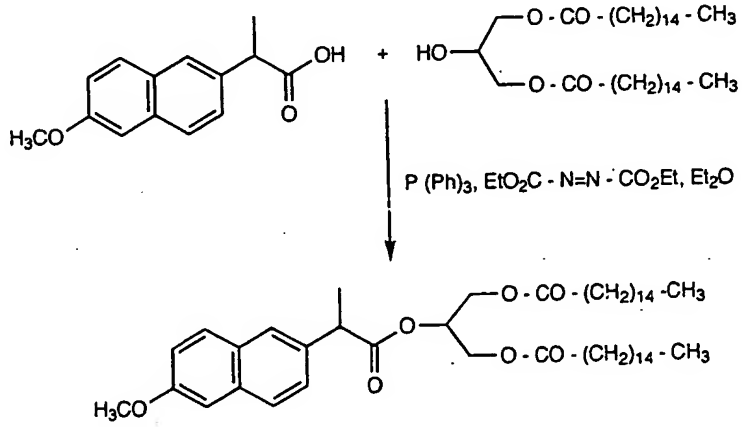

Fig. 31.6 Synthesis of the naproxen-2-glyceride.[43]

The rationale for the design of lipoidal prodrugs is based on well-established principles concerning the intestinal absorption of natural triglycerides.[43,44] As described by Jones[43] (see Fig. 31.7):

> Orally ingested fat enters in the intestinal tract and, as a result of the churning action of stomach musculature, forms an oil-in-water emulsion which passes down the duodenum where it comes into contact with pancreatic lipase. This enzyme acts at the interface of the emulsion particles and specifically cleaves the triglycerides, releasing the fatty acids derived from the 1 and 3 positions, giving 2-monoglycerides as the predominant product. The 2-monoglycerides, free fatty acids and bile salts form negatively charged polymolecular aggregates termed micelles. Only small quantities of diglycerides and triglycerides are present in these micellar particles, but these quantities can apparently be absorbed intact. During the conversion of fats from an emulsion phase (diameter 5000 Å) to a micellar phase (diameter 40–50 Å), the particle size has been greatly decreased. These micellar particles are now small enough to allow free access to the microcillous spaces and absorption into the mucosal cell, where resynthesis occurs under the influence of intracellular enzymes. The triglycerides are finally released from the mucosal cells to the lymphatic circulation as chylomicron particles.

Glyceride prodrugs were also prepared starting from aspirin,[45,46] indomethacin,[47] chlorambucil,[48] and GABA.[49,50] An extension of the use of lipoidal transport groups was made to phospholipids.[51,52] Despite their interest, lipoidal prodrugs have low chances being developed, mostly because they do not crystallize well and can be obtained pure only with difficulty.

The widespread use of acyloxymethyl esters in antibiotic chemistry, as illustrated above for bacampicillin, was initiated by Jansen and Russel[53] at Wyeth Laboratories and successfully applied to pivampicillin,[20] talampicillin[22] and cephalosporins.[54] In each of these cases, the oral absorption of the antibiotic was improved by some 2–3-fold over that of the parent compound. The acyloxymethyl derivatization was also extended to amino acids such as α-methyldopa,[55] isoguvacine[56] and tranexamic acid,[57] anti-inflammatory drugs such as niflumic acid[58] or indomethacin,[59] and quinolone antibacterials such as norfloxacin.[60]

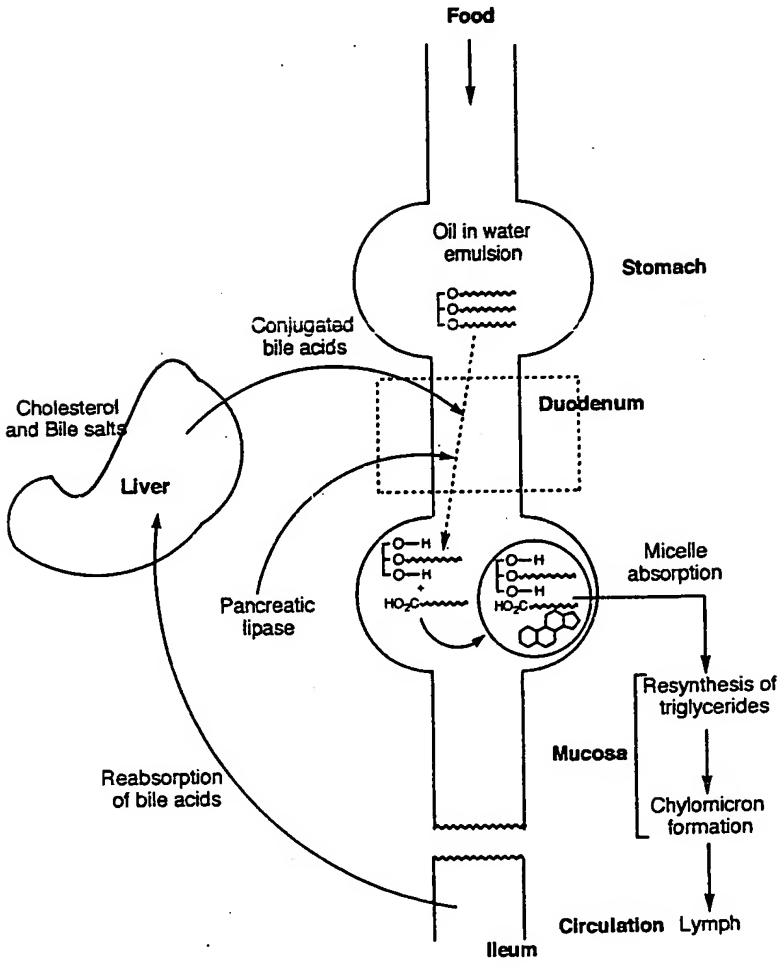

Fig. 31.7 Absorption of fats in the gastrointestinal tract.[43]

Primary amides of carboxylic acids are easily converted in humans to the corresponding acid (e.g. depamide, progabide) and can thus be used in prodrug design. Amides of ketoprofen-derived arylacetic acids possess a therapeutic index one order of magnitude greater than that of indomethacin.[61]

4. *Derivatization of amines*

Owing to the slow *in vivo* cleavage rate of the *N*-substituted amides, acylation of amines is generally not recommended. Better possibilities are offered by activated amides, peptides, imines and soft quaternary ammonium salts. However, the use of simple *N*-acyl derivatives must not be systematically discarded. The *N*-benzoyl or *N*-pivaloyl derivatives of the inhibitory neurotransmitter GABA are examples of compounds able to penetrate the blood–barrier and to abolish pentetrazole- and bicuculline-induced convulsions. It was also demonstrated in rats that, following subcutaneous injection, rat-brain homogenates liberate free GABA from these

amides.[62] There is even some biochemical and pharmacological evidence suggesting that *N*-pivaloyltaurine crosses the blood–brain barrier.[63]

Imines[64] and enamines,[65,66] stabilized through hydrogen bonds, can also be effective prodrugs of primary amines (Fig. 31.8).

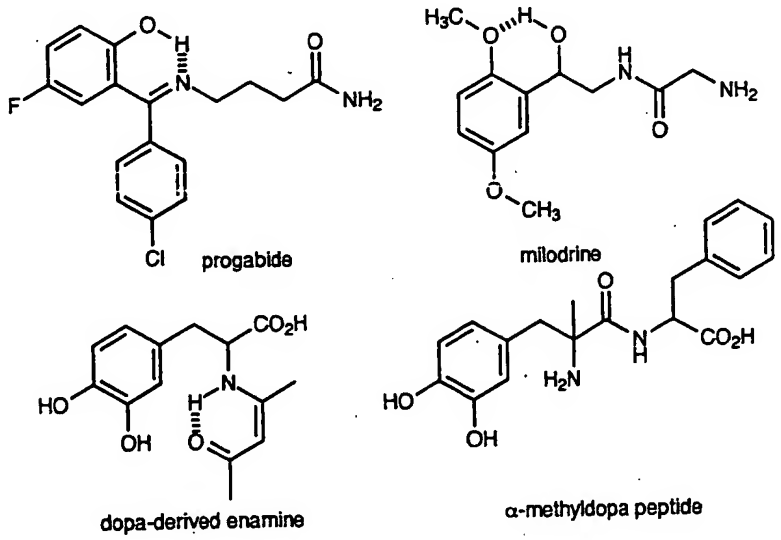

Fig. 31.8 Imine, enamine and peptide prodrugs derived from amino functions.

Small peptides constitute an alternative way of derivatizing amines. The hypotensive drug milodrine, for example (Fig. 31.8), is the well-absorbed transport from which 2-(2,5-dimethoxyphenyl)-2-hydroxyethylamine (ST-1059) is liberated by enzymic cleavage of the glycine residue.[67] Given orally to fasted Wistar rats, the *N*-(*Z*-alanyl)amide of the hypoglycaemic sulfonylurea carbutamide demonstrated a 4–6 times higher potency than the parent sulfonamide. The compound is well tolerated and is metabolized to the parent drug, the amino acid moiety just modifying the bioavailability.[68] Among the numerous variations made around the α-methyldopa molecule, acylation with a glycyl-glycyl residue was claimed to improve the oral bioavailability.[69] For a series of anticandidal di- and tripeptides containing *m*-fluorophenylalanine (m-FPhe), competitive antagonism studies supported peptide transport-mediated entry of the warhead m-FPhe inside the cell.[70] Dipeptides derived from α-methyldopa (Fig. 31.8) show a 10–20-fold better penetration of the intestinal wall than α-methyldopa itself.[71]

5. *Prodrugs for compounds with acidic NH functions*

Prodrugs obtained by *N*-alkoxycarbonyloxymethylation of 5-fluorouracil show improved delivery properties. Both 1- and 3-alkoxycarbonyloxymethyl derivatives are hydrolysed quantitatively to 5-fluorouracil but the 3-substituted derivatives show greater promise as prodrugs since they combine adequate stability in aqueous solution with a high susceptibility to hydrolysis in plasma.[72] Sulfonamides, but also carboxamides, carbamates and other NH-acidic compounds (Fig. 31.9) can be acylated with various groups[73] or converted into phthalidyl derivatives.[74]

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B. Site-specific d

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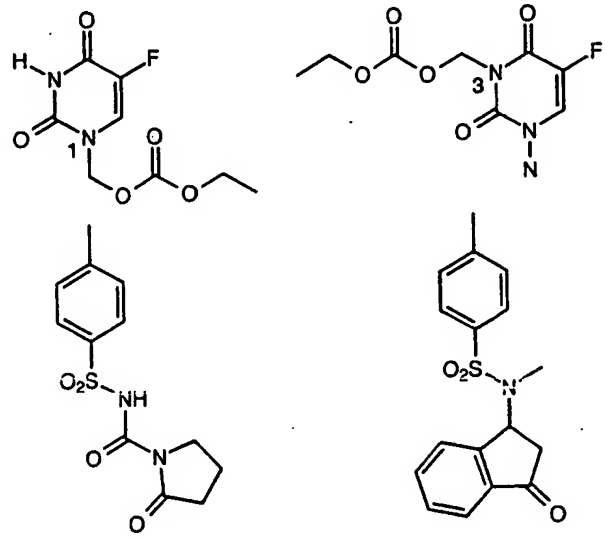


Fig. 31.9 Prodrugs of acidic NH functions.

Hetacillin[75,76] and droxicam[77] are examples of simultaneous cyclic protections of an acidic NH function and an amino or a hydroxylic groups located in the vicinity (Fig. 31.10).

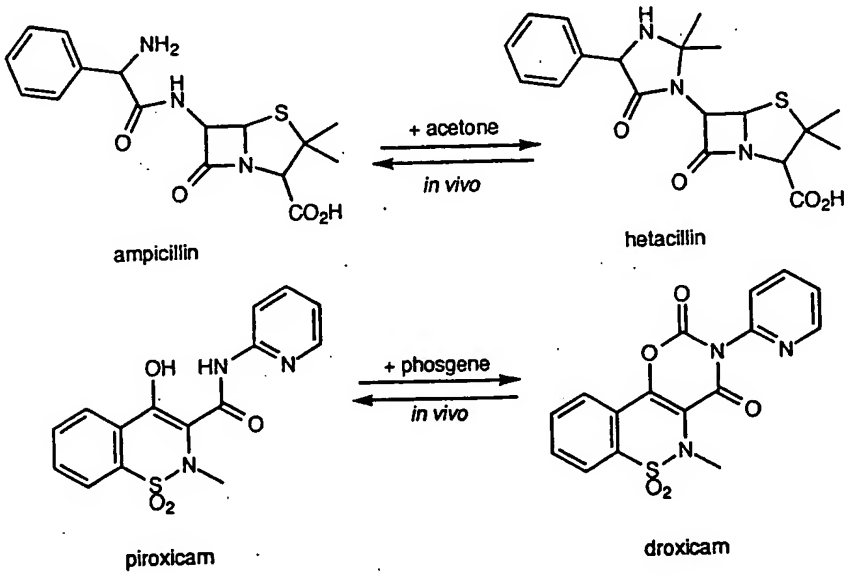


Fig. 31.10 Cyclic protections of two neighbouring functions.

B. Site-specific delivery

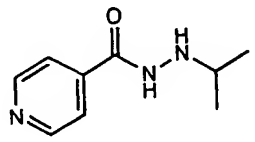
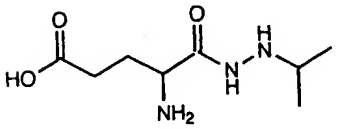
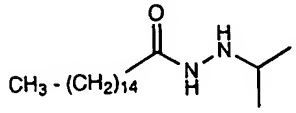
Many hopes were put in the prodrug approach as a means to achieving the targeting of drugs for specific sites in the body. Actually only a few convincing examples are found in the literature and we are becoming somewhat disillusioned about the real possibilities of the approach. In

principle two targeting possibilities can be considered:[25] first, one can design a prodrug that affords an increased or selective transport of the parent drug to the site of action (*site-directed* drug delivery); second, one can design a derivative that goes everywhere but undergoes bioactivation only inside the target organ (*site-specific* drug release).

1. Site-directed drug delivery

Most of the successes in achieving site-directed drug delivery through prodrugs have been through localized delivery of lipophilic prodrugs (eyes, skin) with increased permeability characteristics. Systemic site-directed delivery, that is delivery to a specific internal site or organ through selective transport, is very difficult to achieve. Nevertheless, some possibilities of local enrichment or of privileged entry into the central nervous system are found in the literature. Thus the L-glutamic analogue of iproniazid presents preferential monoamine oxidase inhibition in the brain,[78] whereas the palmitoyl isopropylhydrazide demonstrates clear cardiac selectivity (Table 31.1).

Table 31.1 Effect of the acyl group in isopropyl hydrazide on selective transport.[78]

Isopropyl hydrazide	% Monoamine increase		Ratios
	Cardiac catecholamines	Cerebral 5-HTP	
	100	100	1.0
	75	250	3.3
	145	60	0.4

The propensity of fatty chains to concentrate in cardiac tissue is also illustrated by findings in the field of myocardial imaging agents. An iodine- and tellurium-containing fatty acid (Fig. 31.11) has a high heart uptake, and heart/blood ratios remained high for several hours: 13 : 1 after 1 hour and 9 : 1 after 4 hours.[79]

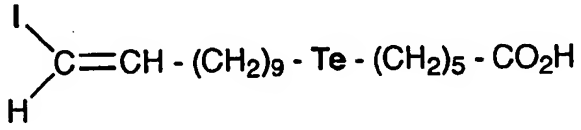


Fig. 31.11 Myocardial imaging agent.

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Coupling of drugs to modified bile acids was recently proposed for liver-specific targeting.[80] The rationale is based on the recognition of bile acid-linked drugs by the endogenous bile acid transport system. Chlorambucil, an alkylating cytostatic agent, HR-780, an inhibitor of HMG-CoA reductase, and an oxaproline peptide, an inhibitor of prolyl-4-hydroxylase, were chosen for conjugation to bile acids (Fig. 31.12).

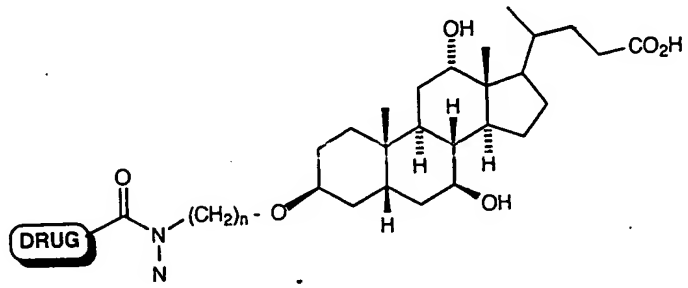


Fig. 31.12 Bile acids for liver specific targeting.[80]

The 2,3-dichlorophenoxyacetic moiety of ethacrynic acid was claimed to have a high affinity for the renal tissue,[81] and 2-thiouracil and 6-propylthiouracil exhibit marked affinities for melatonin-producing tissues.[82,83] They were therefore (unsuccessfully) tested for the treatment of malignant melanoma.[84] Many other examples of selective conducting moieties are found in X-ray contrast media and radioisotope imaging agents.[85] Similar efforts were made to find selective cancer chemotherapeutics, and a variety of drugs that are known to accumulate selectively in particular tissues have also been tried. Mustard derivatives of amino acids, steroid hormones, tetracyclines, quinacrine and uracil are examples.[86] Site-directed cancer chemotherapy can involve drugs bound to specific antibodies. Daunomycin, conjugated via an oxidized dextran bridge with anti-B-cell lymphoma 38C-13 cell-surface IgM antibodies, given to 38C-tumour-bearing mice gave increased life span and even complete cure.[87] Descriptions of some other attempts to achieve delivery to the central nervous system will be found in Chapters 37 and 38.

2. *Site-specific drug release*

The whole strategy of site-specific release of a given drug lies in the discovery of an enzyme present in high concentrations in the target organ and effectively absent elsewhere. An appropriate prodrug can then be designed using the selective cleavage possibility offered by the enzyme.

A selective renal vasodilatation, for example, is produced by administration of γ-glutamyldopa. It is well known that L-dopa is a precursor of the neurotransmitter dopamine, which plays an important role in the central nervous system and in the kidneys. The association of L-dopa with a peripheral dopa-decarboxylase inhibitor allows preferential dopamine production in the brain and can be considered at present the best therapeutic possibility for Parkinson's disease.

On the renal side, a prodrug of L-dopa, γ-glutamyl-L-3,4-dihydroxyphenylalanine (γ-glutamyldopa), produces a specific vasodilatation of the renal tissue. Indeed, the γ-glutamyl derivatives of amino acids and peptides accumulate in the kidneys, where they undergo a

selective metabolic process (for a review see Magnan *et al.*[88]). The successive actions of two enzymes present in high concentration in the kidney, γ-glutamyl transpeptidase and L-aromatic amino acid decarboxylase, release dopamine locally from γ-glutamyldopa (Fig. 31.13).

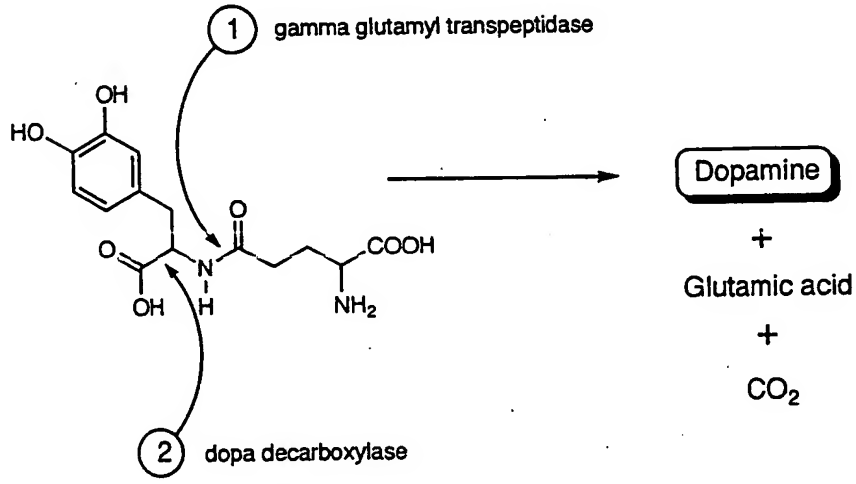
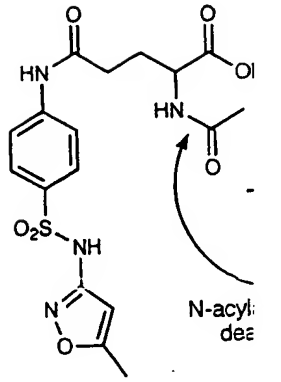


Fig. 31.13 Selective renal vasodilatation with γ-glutamyl-dopa.[89]

In mice, the renal levels of dopamine, after γ-glutamyldopa, are five times higher than after an equimolar administration of L-dopa. A perfusion of 10 μM g^{-1} per 30 min of γ-glutamyldopa in rats produces a 60% increase of the renal plasmatic flux.[89] The same dose of L-dopa induces no vasodilatation. Massive administration of γ-glutamyldopa (20 times the preceding dose) produces only a weak pressor effect, demonstrating that the systemic effects of the prodrug are low. The same principle was used for the synthesis of γ-glutamyl derivatives of dopamine itself and diacyldopamines.[90,91]

Similarly, it is possible to obtain a kidney-selective accumulation of sulfamethoxazole by administering the drug in the form of *N*-acetyl-γ-glutamate.[92] The regeneration of the free sulfamide requires the initial deacylation of the glutamic moiety thanks to an *N*-acylamino acid deacylase which is also present in the kidney in high concentrations (Fig. 31.14). The γ-glutamyl strategy for confining drug action to the kidney and the urinary tract implies that the prodrug under consideration can function as a substrate for γ-glutamyl transpeptidase and, eventually, for *N*-acylamino acid deacylase.

The unique glucosidase activity of the colonic microflora has been utilized to deliver selectively steroid prodrugs useful in treating inflammatory bowel disease.[93] Dexamethasone 21-β-D-glucoside appeared to be a good candidate as nearly 60% of an oral dose of the prodrug reached the caecum in the form of free steroid. Given orally, the parent dexamethasone was absorbed almost exclusively from the small intestine and less than 1% reached the caecum.[94] In various tumour tissues the activity of the enzyme uridine phosphorylase is markedly higher than in the surrounding normal tissues. This observation prompted the synthesis of 5-fluorouracil prodrugs. Among them, 5′-deoxy-5-fluorouracil shows high antitumour activity and less host toxicity compared to fluorouracil. This favourable therapeutic index is attributed to a preferential bioactivation by uridine phosphorylase in the tumour cells.[95,96]



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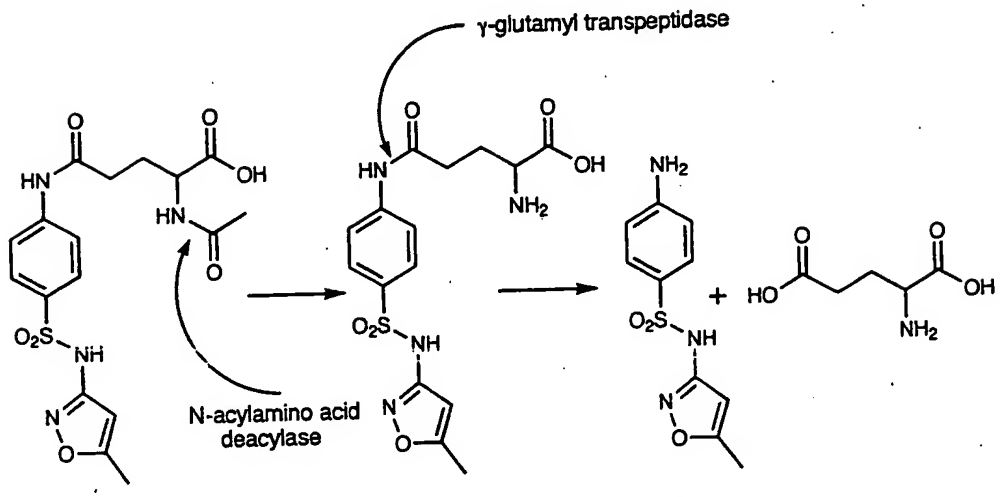

Fig. 31.14 Kidney-selective release of sulfamethoxazole.[92]

C. Prolonged duration of action

Unless they are accumulated in the fatty tissues, orally administered drugs are not expected to act much longer than their transit period in the gastrointestinal tract (12–48 h). For drugs rapidly cleared from the body, the duration of activity is even shorter, and a frequent dosing within the 24-h period is required to maintain adequate plasma concentrations. This frequent dosing of short-half-life drugs results in sharp peak–valley plasma concentration–time profiles, and consequently patient compliance is often poor.[97] However, for therapeutic, epidemiological, sociological or political reasons, durations of action prolonged over weeks or months are desired. The easiest administration route is then represented by intramuscular injection of depot preparations. The most successful applications are found in the domains of hormonal steroids, of antipsychotic drugs and, to a lesser extent, of antibiotics. The general strategy consists in preparing lipophilic prodrugs, dissolved or suspended in oily vehicles, and administering them by deep intramuscular injection.

1. *Contraceptive steroids*

Progestogens such as norethysterone enanthate and medroxyprogesterone acetate (MPA) have long durations of activity (3 months) owing primarily to slow release from the injection site and storage in the fatty tissues.[98] Progestogen–estrogen combinations such as dihydroxyprogesterone acetophenide–estradiol enanthate or MPA–estradiol cypionate (=cyclopentylpropionate) are administered on a monthly basis.

2. *Treatment of menopause*

The symptomatic treatment of menopause (sweating, hot flushes, depression) has been successfullly accomplished by the use of 200 mg of dehydroepiandrostereone-3-heptanoate and 4 mg of estradiol 17-β-valerate in a suspension of a castor oil–benzyl benzoate vehicle.[99]

In the estradiol prodrug estradiol 3-benzoate 17-β-cyclooctenyl ether (EBCO), the phenolic hydroxyl group is masked as a benzoyl ester and the alcoholic 17-γ-hydroxyl as an enol ether derived from cyclooctanone (Fig. 31.15). Given to rats orally as a suspension in sesame oil, this derivative was active for 1 to 2 weeks because it was stored in body fat.[100]

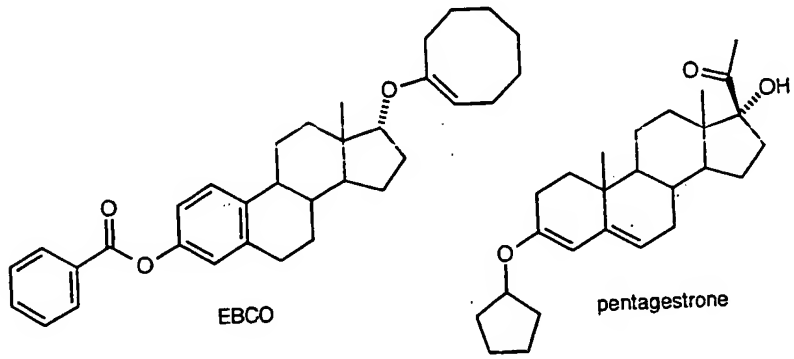

Fig. 31.15 Enol ethers as long-lasting steroid prodrugs .[100,101]

Enol ethers were also used for the synthesis of other long-lasting steroidal drugs such as penmestrol or pentagestrone.[101]

3. *Antipsychotics*

Clinically, depot neuroleptics possess several advantages over the short-acting oral forms. Among these, the main advantages are (a) ease of administration, (b) reliable therapeutic effect with no increase in tolerance, (c) enhanced patient compliance, (d) reduced relapse and rehospitalization rate, and (f) enhanced rate and incidence of 'normal life' reintegration and resocialization.[98]

IV. THE USE OF CASCADE PRODRUGS

Classical carrier-linked prodrugs may sometimes be ineffective because the prodrug linkage is too stable (amides, nonactivated esters). In such cases a β-assistance provided by a nuclophile easily generated *in vivo* can represent an interesting solution. The release of the active molecule from the prodrug proceeds through a two-step trigger mechanism for which the name 'cascade latentiation' was coined by Cain in 1975.[102,103]

The concept, also called distal hydrolysis[34] or the double prodrug concept,[25,106] is illustrated by the use of 2-acyloxymethylbenzoic acids as amine protective functions providing amides with the lability of esters (Fig. 31.16A) and by the use of substituted vinyl esters [= (2-oxo-1,3-dioxol-yl)methyl esters] as lipophilic cascade carriers for carboxylic acid-containing drugs such as ampicillin[104] or α-methyldopa[105] or various cephalosporins[12,21,30,107] (Fig. 31.16B).

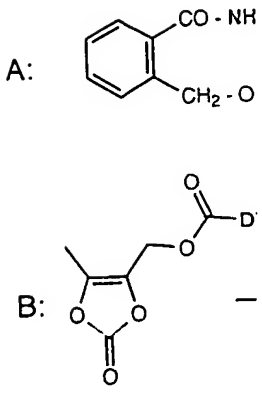

Fig. 31.16 (A) 2-Acyloxymeth
esters as lipophilic cascade carrier

A. Water-soluble

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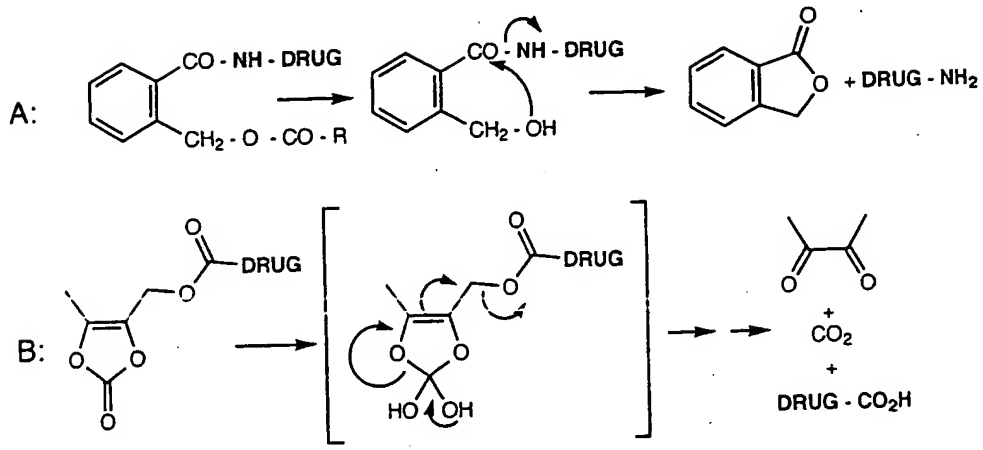


Fig. 31.16 (A) 2-Acyloxymethylbenzoic acids provides amides with the lability of esters.[102,103] (B) Substituted vinyl esters as lipophilic cascade carriers for carboxylic acid containing drugs.[104,105]

A. Water-soluble taxol prodrugs

Taxol is a potent microtubule-stabilizing agent that has been approved for cancer treatment. Despite taxol's therapeutic promise, its aqueous insolubility (<0.004 mg ml^{-1}) hampers its clinical application. Nicolaou *et al.*[108] report the design, synthesis and biological activity of prodrugs designed to improve water solubility and which can also be considered as cascade prodrugs (Fig. 31.17).

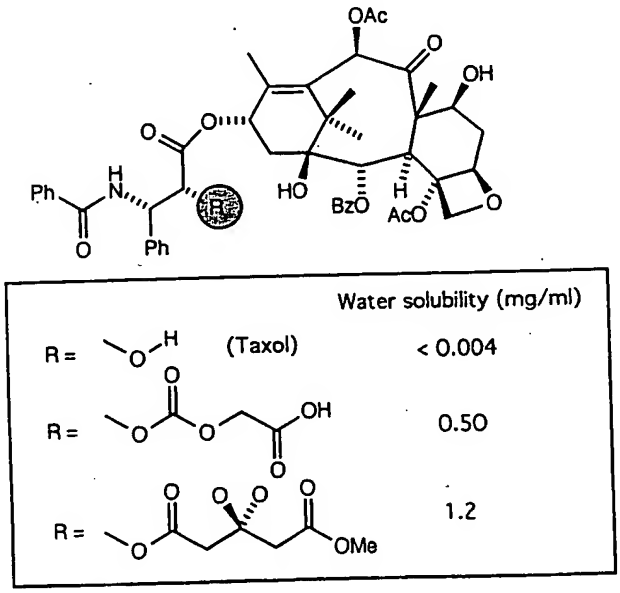


Fig. 31.17 Water-soluble protaxols.[108]

The mechanistic rationale of the design of these protaxols lies in the spontaneous decomposition of the carbonate ester after the abstraction of one of the activated protons or of an acidic proton (Fig. 31.18).

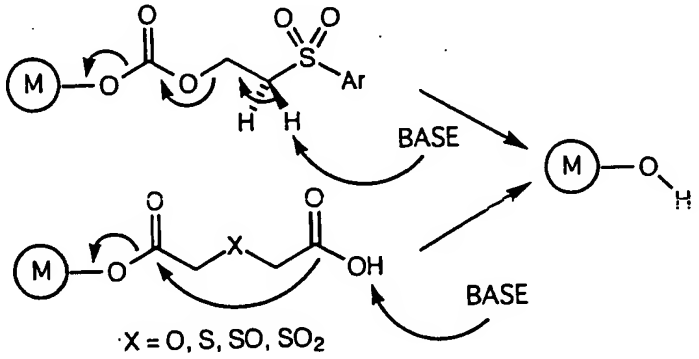


Fig. 31.18 Taxol release mechanisms from protaxols.[108]

B. Bioactivation of an antibacterial prodrug

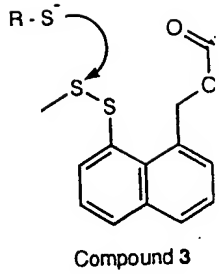
Although the amino acid (**1**) in Fig. 31.19 is a potent inhibitor of CMP-KDO synthetase, a key enzyme in the biosynthesis of the lipopolysaccharide of Gram-negative bacteria, it is unable to reach its cytoplasmic target and is therefore inactive as an antibacterial agent. Simple lipophilic esters are not useful for enhancing the delivery of the amino acid (**1**) since they are not cleaved by the bacteria. The double prodrug (**3**) on the other hand, has recently been found to solve the problem.[109] Upon entry into bacterial cells, the disulfide bond in compound (**3**) is reduced by sulfydryl compounds present in the intracellular milieu, resulting in the formation of the thiol (**2**). This is highly unstable and the active amino acid (**1**) is formed by a rapid intramolecular displacement.

C. Double prodrugs derived from pilocarpine

Monoesters of pilocarpic acid are potentially useful prodrug forms for ocular administration and enable an efficient penetration through the corneal membrane. Unfortunately, they suffer from poor solution stability as in aqueous solution they cyclize spontaneously to pilocarpine.[110] However, double esters derived from pilocarpic acid (Fig. 31.20) possess high stability in aqueous solution (shelf-lives of more than 5 years at 20°C were estimated). At the same time, they are readily converted to pilocarpine under conditions simulating those occurring *in vivo* through a sequential process involving enzymatic hydrolysis of the *O*-acyl bond followed by spontaneous lactonization of the intermediate pilocarpic monoester.[111]

D. Double prodrugs for peptides

Amsbery and Borchard[112,113] have applied Cain's cascade concept to prepare lipophilic



Compound 3

Fig. 31.19 Bioactivation of th
cytidylyltransferase.[109]

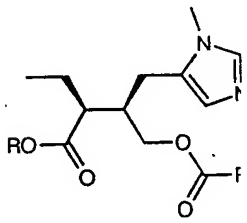


Fig. 31.20 Double esters
simulating those occurring *in*

polypeptide prodrugs. T
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step is highly favoured
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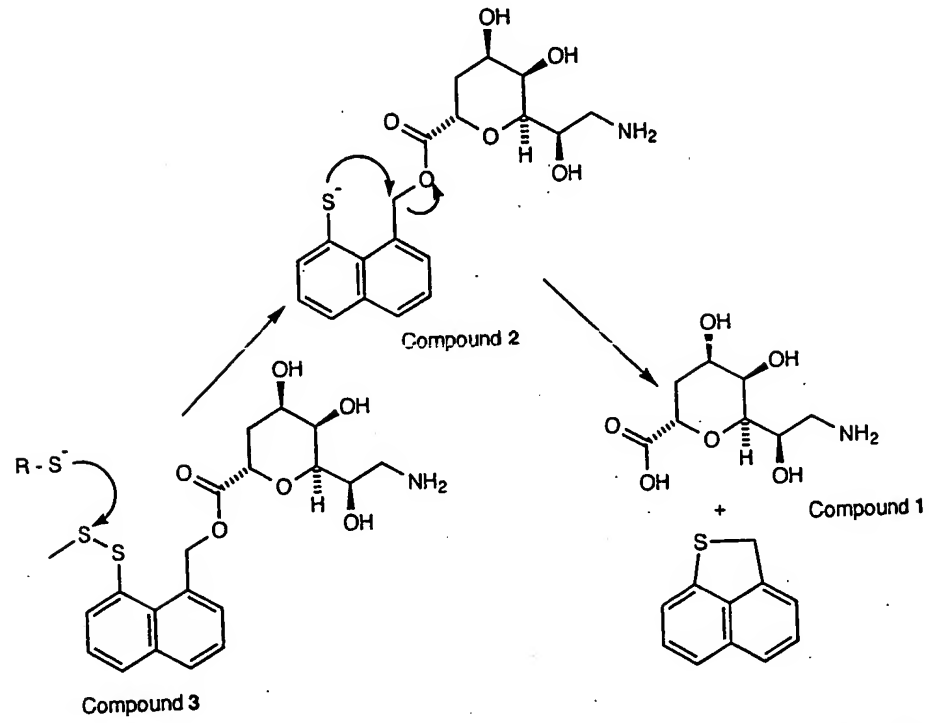

Fig. 31.19 Bioactivation of the antibacterial prodrug of an impermeant inhibitor of 3-deoxy-D-manno-2-octulosonate cytidylyltransferase.[109]

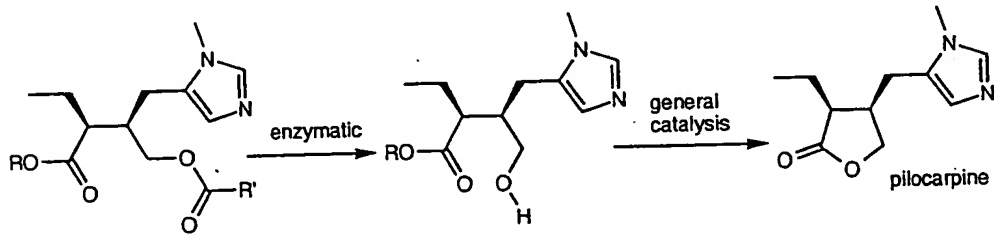

Fig. 31.20 Double esters derived from pilocarpic acid are readily converted to pilocarpine under conditions simulating those occurring *in vivo*.[111]

polypeptide prodrugs. The amine functionality of the polypeptide is coupled to 2′-acylated derivatives of 3-(2′,5′-dihydroxy-4′,6′-dimethylphenyl)-3,3-dimethylpropionic acid (Fig. 31.21). Under simulated physiological conditions the parent amine is regenerated in a two-step process: enzymatic hydrolysis of the phenolic ester, followed by a nonenzymatic intramolecular cyclization leading to the release of the free amine (polypeptide) and a lactone. The lactoniztion step is highly favoured because of the steric pressure created by the three methyl groups ('trimethyl lock' concept). An alternative to the hydrolytic first step involves a bioreductive generation of the intermediate phenolic amide (Fig. 31.21).

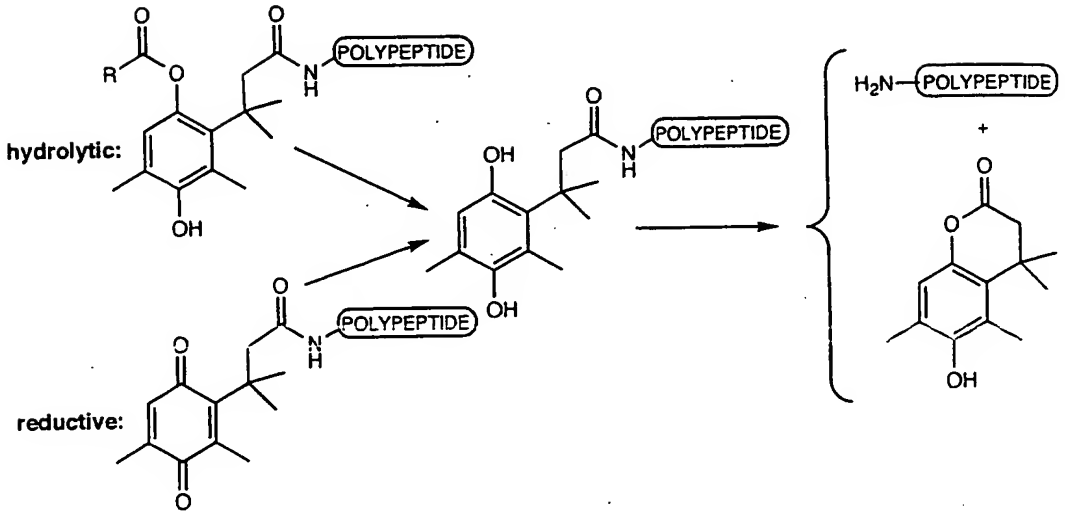

Fig. 31.21 Proposed conversion of esterase-sensitive and redox-sensitive double prodrugs of peptides.[112,113]

V. SOFT DRUGS

The 'soft' quaternary ammonium salts developed by Bodor[114–117] are vulnerable derivatives of their 'hard' analogues. In general, they show the same type of activity but with a much shorter half-life, as is the case for the soft analogue of cetylpyridinium chloride (Fig. 31.22). Both compounds have the same hydrophobic chain length, and thus similar surface-active and antimicrobial properties. However, the soft analogue is about 40 times less toxic than its hard analogue in terms of LD_{50}.[115] This is because the soft analogue undergoes a fast and easy hydrolytic deactivation resulting in the simultaneous destruction of the positive quaternary head and the surface-active properties.

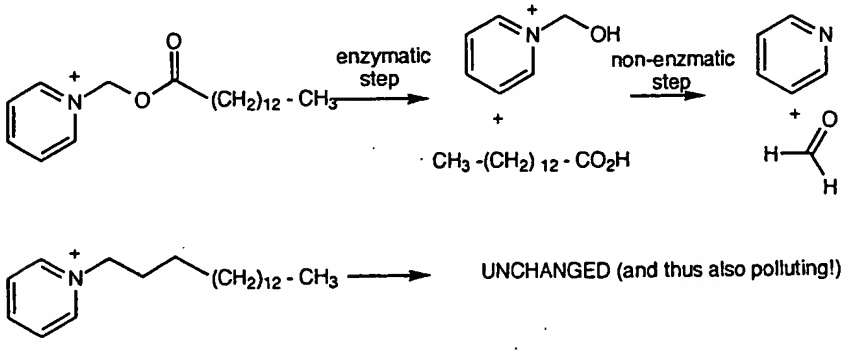

Fig. 31.22 The soft analogue of cetylpyridinium chloride.[115]

In a similar way, the te
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31.23). The correspondin
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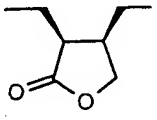

Fig. 31.23 The soft quatern

VI. CONCLUSION

The carrier-prodrug appı
improvement of some
convincing; they have ne
art'.[119] Probably most of
carrier-prodrugs represent
groups in organic chem
imagination has no limit
candidates, only very few

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In a similar way, the tetradecyloxymethyl quaternary salt of pilocarpine allows enhanced penetration through the cornea followed by a facile hydrolytic cleavage to pilocarpine (Fig. 31.23). The corresponding hard analogue (*N*-cetylpilocarpine) is unable to regenerate the parent drug and lacks any activity.[118]

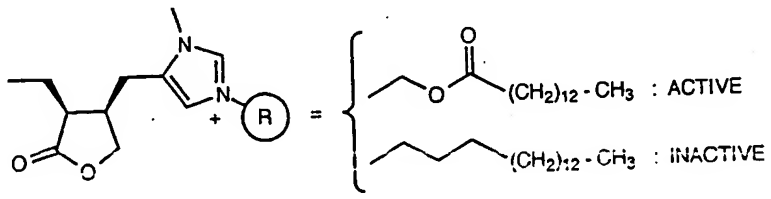

Fig. 31.23 The soft quaternary derivative of pilocarpine allows an enhanced penetration through the cornea.[118]

VI. CONCLUSION

The carrier-prodrug approach is particularly successful in the antibiotics field and in the improvement of some pharmacokinetic parameters. Other prodrug examples are less convincing; they have nevertheless been included in this chapter to illustrate the 'state of the art'.[119] Probably most of them have never been tested in man or laboratory. The design of carrier-prodrugs represents in medicinal chemistry the counterpart of the design of protective groups in organic chemistry. The approaches have much in common; in both of them imagination has no limits and reigns as master. However, among the enormous number of candidates, only very few attain real success and celebrity.

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